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ART in Endometriosis

Dr. Baidyanath Chakravarty

Introduction

Endometriosis is an enigmatic disease. The incidence is around 0.5 to 5% in fertile and 25-40% in infertile women. Various theories have been suggested for genesis of endometriosis. These are: - inflammatory, immunologic, hormonal and genetic. The clinical problems of endometriosis are – pain (dysmenorrhoea, dyschezia, dyspareunia etc), volume of the disease and subfertility. The gold standard for diagnosis of endometriosis is laparoscopic examination of pelvic organs, which of course introduces an element of bias when studying prevalence of endometriosis in different groups of women. However, high prevalence of endometriosis has been recorded in women with chronic pelvic pain (around 33%) and subfertility (30-50%).[1]

Several mechanisms have been suggested to explain the low fertility rate in women with endometriosis. These are, altered folliculogenesis resulting in reduced oocyte quality;[2,3] mechanical interference with oocyte pickup and transport;[4] exposure to a hostile environment of macrophages, cytokines and vasoactive substances in the peritoneal fluid,[5,6,7] suboptimal endometrial receptivity and anatomical dysfunction and distortion of the fallopian tubes and ovaries.

Women with endometriosis often require ART for their infertility treatment. More than one in three woman undergoing IVF has endometriosis.[8] Severity of endometriosis may have an adverse impact on IVF outcome.[5,9]

But, impact of severity of endometriosis on IVF outcome is still debated. Pre-ART conservative surgery specially for endometrioma is currently a controversial topic. Adenomyosis and recto-vaginal septum nodules are frequent associations of severe grades of endometriosis and if left untreated may have an adverse impact on ART outcome. Similarly, deep infiltrating endometriosis, extent of pelvic adhesion (mild or severe) may have individual

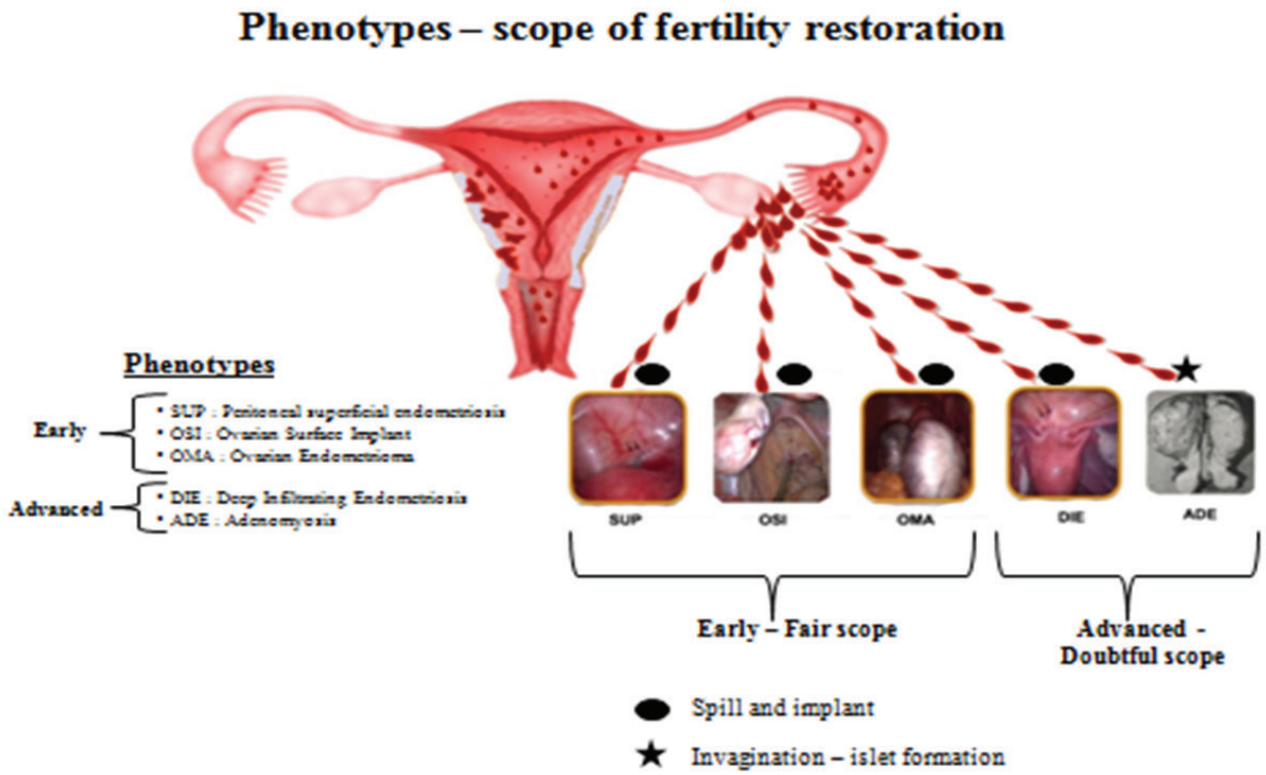


Diagram-1: Classification – phenotypes – prognosis of treatment

influence on outcome of ART treatment. These different phenotypes associated with advanced endometriosis need pre-ART treatment to optimize pregnancy outcome.

In this chapter, an attempt has been made to outline broadly the role of ART in infertility management in general with special emphasis on – how far pre-ART conservative surgical or medical management may positively enhance outcome of ART in endometriosis associated infertility management.

In addition, the impact of ART on symptom progression of endometriosis and pregnancy outcome in women achieving pregnancy following ART treatment will be briefly outlined in the later section of this chapter.

Classification of endometriosis:

Endometriosis has been classified into five phenotypes:

a) Superficial peritoneal endometriosis
b) Ovarian surface implants
c) Ovarian endometrioma
d) Deep infiltrating endometriosis
e) Adenomyosis

These phenotypes have been broadly categorized as 'early' and 'advanced' rather than ASRM classification which helps in determining prognosis of the fertility enhancing treatment by ART:

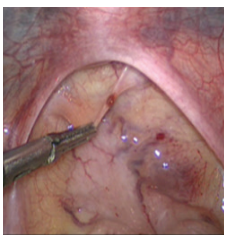
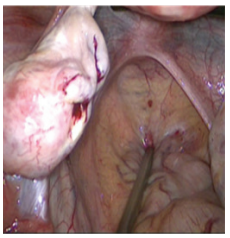
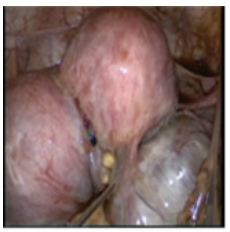
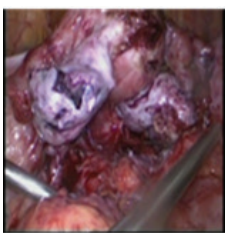
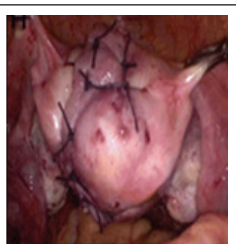
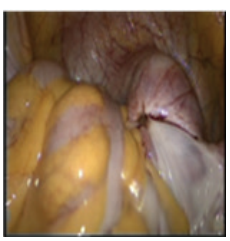
ART in early endometriosis:

Of the four phenotypes outlined above, early endometriosis includes two categories – superficial peritoneal implant and ovarian surface implant with 'no' or 'mild' adhesion. This group responds most favourably to any type of fertility enhancing treatment of endometriosis like ovulation induction, IUI or IVF (to be discussed later).

But the other group, categorized as advanced endometriosis includes –deep invaginating ovarian endometriosis (endometrioma) with mild or dense adhesion, deep pelvic cellular tissue infiltration with severe adhesion. These two groups have doubtful scope of response to available forms of treatment of fertility restoration in endometriosis. Other two subgroups namely adenomyosis and combination of the above group designated as 'frozen pelvis' have doubtful or hopeless scope of response to any type of fertility restoration treatment including ART.

The following diagrams with legends summarize scope of fertility restoration following ART in different groups and subgroups enumerated above.

Diagram-2

Early Endometriosis		
Superficial Peritoneal implant		**Fair Scope**
Ovarian surface implant - with no or flimsy adhesion		
Advanced Endometriosis		
Deep invaginating ovarian endometriosis - endometrioma with flimsy or dense adhesion		**Doubtful Scope**
Infiltrating endometriosis with mild to severe adhesion		
Adenomyosis - with mild or dense adhesion		**Doubtful to hopless scope**
Combined - "frozen pelvis"		

Incidence of different stages:

In practice, the incidence of severe or advanced endometriosis is relatively higher compared to the incidence of early endometriosis. This is because of delay in diagnosis and/or not performing laparoscope in routine investigation of unexplained infertility. The stage wise incidence is given below[10] –

- Gr-IV or severe in 30%
- Gr-III 30%

} Advance

- Gr-II 23%
- Gr-I 15%

} Early

Causes of infertility in endometriosis –

Primarily mechanisms of endometriosis related subfertility are as follows:[11]

- Interference with oocyte development or disturbance in early embryogenesis
- Impaired fertilization
- Reduced endometrial receptivity
- Distortion of adnexal anatomy or destruction of adnexal organs inhibiting ovulation or ovum capture after ovulation

Apart from anatomical distortion and to some extent destruction of pelvic organs (as in advanced endometriosis) the precise pathologic mechanisms of endometriosis related subfertility – specially in early stages remain unclear. Perhaps the effect associated with inflammatory changes in the peritoneal fluid, persist in all stages of endometriosis which may be responsible for infertility in these women. The inflammatory changes involve increased activity of macrophages resulting in enhanced phagocytosis and secretion of growth factors, cytokines and prostaglandins.[12] These secretory products have been indirectly implicated in adverse effects on fertility and in stimulating the implantation and proliferation of endometrial cell in the peritoneal cavity transported via retrograde flow of menstrual blood (Samson's theory). In the follicular fluid of women with endometriosis, the level of vascular endothelial growth factor is decreased and levels of interleukine-1, other pro-inflammatory cytokines, natural killer cells, b-lymphocytes and monocytes are elevated. Some of these factors have been associated with poor quality oocytes and are responsible for inducing apoptotic changes and oxidative stress in the surrounding granulosa cell.[13]

It has also been suggested that increased peritoneal prostaglandin concentration may play a role by interfering with ovulation, altering tubal peristalsis, reducing sperm motility or increasing uterine contractility (thereby interfering with implantation of the blastocyst). There is also a theory that the altered peritoneal milieu due to presence of increased amount of macrophages, T-lymphocytes and their mediators may destroy spermatozoa and oocyte and may impair fertilization.

Severe endometriosis can cause or aggravate sub-fertility via several mechanisms. Pelvic pain and dyspareunia may discourage or reduce coital frequency. Adhesions may also cover or distort the anatomical relationship between fallopian tubes and ovaries. Ovarian endometriomas may be so extensive that they may destroy ovarian cortex and may lead to oligo or anovulation.

Therapies currently available for improvement of fertility in endometriosis:

Currently the treatment of endometriosis for improvement of fertility can be categorized in five broad groups –

a) Expectant
b) Medical

} Neither desirable nor effective

c) Surgical
d) Combination medical and surgical
e) ART

} Effective either individually or in combination

Expectant and Non-ART management:

Pregnancy rates in endometriosis do not improve either following expectant or no treatment or medical management of endometriosis. Some investigators have considered these women to be part of a group of couples with essentially unexplained infertility. But the probability of spontaneous pregnancy or even with simple superovulation with clomiphene or letrozole among women in early endometriosis is lower than amongst couples with unexplained infertility.[14] Our experience with these types of treatments is detailed in Table-1.

TABLE 1:

TYPES OF TREATMENT	NO	CL. PREG	VIABLE DELIVERY
Surgical Ablation/Coagulation (Bipolar) (Active)	45	10 (22.2%)	8 (17.7%)
Expectant or 'No' Treatment / OI	30	7 (23.3%)	6 (20%)

Comments:

1. Benefit of laparoscopic ablation of endometriotic implant for improving pregnancy rate is doubtful
- But progression of disease (10%) may be arrested (Opoien et al, 2011)
- No role of medical treatment like GnRH analogue, Danazole – delays conception

However an expectant approach may be considered in young couples for upto two years. But undue delay should be avoided when the woman is aged over 35 years or there are other factors contributing to sub-fertility. Benefit of laparoscopic ablation of endometriotic implant for improving pregnancy rate is also doubtful. This does not exclude the scope of laparoscopic evaluation of a case of either unexplained infertility or unexplained pelvic pain. If endometriotic implants are detected there is definite indication of cauterization or ablation of the implant. The procedure will help at least to reduce the risk of progression of the disease though it may not help in fertility enhancement. Treatment with anti-endometriotic drug like Danazole, GnRH-analogue or Dienogest in the absence of pain or dyspareunia is contraindicated where the couple is eager for a conception.

ART management in early endometriosis:

Pregnancy rate improves following IVF treatment in early endometriosis. But the treatment is also complicated and expensive. Rationally IVF treatment should be attempted when other treatments like super-ovulation or IUI fail to achieve pregnancy. The obligatory indication for IVF in minimal and mild endometriosis is when other infertility factors coexist. Results following IVF is shown in the following Table-2.

TABLE 2:

	NO. OF CYCLES	CLINICAL PREG (n, %)	VIABLE DEL (n, %)
Our Series (2005)	77	27 (35.06%)	19 (24.6%)
Heden et al (2000)	223	85 (38.11%)	67 (30.07%)

Comments:

- Pregnancy rate improves following IVF in early cases
- But expensive as well
- Should be attempted when other treatments fail
- Obligatory indication when other infertility factors co-exist

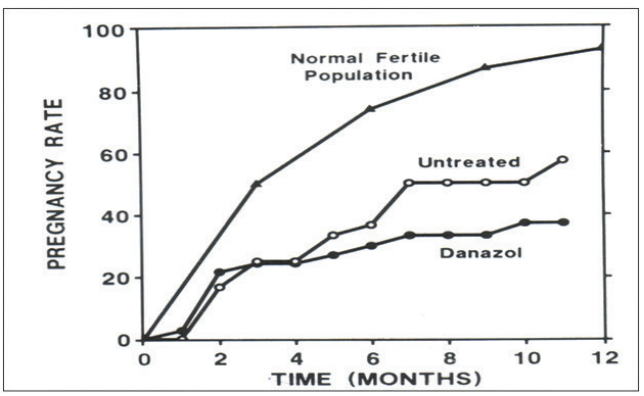
Role of COH-IUI in early endometriosis:

Before ART is attempted, ESHRE guideline (2014)15 has indicated that IUI should always be performed and if three attempts of IUI fail, IVF is the next choice. In fact, instead of expectant or no-treatment and before IVF, IUI-COH is the preferred choice.15 IUI is preferred to 'no' or expectant treatment because even in early endometriosis pregnancy rate is low compared to normal fertile population (Table-3). This is evident from the following diagram (Diagram-3)

TABLE 3: Results of CHO-IUI as against 'No' treatment

	IUI (COH) (n=22)	EXPECTANT (n=25)
Monthly Fecundity	0.15%	0.05%
Cumulative Preg. Rate	37%	24%

Diagram-3: Why IUI is Preferred to 'No' Treatment (Expectant): Pregnancy rate in early endometriosis is low compared to normal fertile population



Summary:

- In early endometriosis, 'NO' or expectant treatment is not desirable
- Laparoscopic ablation or cauterization is doubtful for improvement of fertility; - but may reduce progression (10%) of the disease
- COH-IUI is the preferred choice
- IVF offers better result but expensive as well

ART in advanced endometriosis:

There are three major problems of endometriosis, – more apparent with advanced than with early endometriosis. These are – Pain, volume or extent of the disease and sub-fertility. Pain is experienced by the patients in several forms – the commonest are – dysmenorrhoea, dyspareunia, dyschezia and continuous nagging pain in lower abdomen which may persist throughout the month. Medical treatment may offer some relief for pain and to some extent may also help to reduce the volume of the disease but has no effect on improvement of fertility potential. In fact, so long as the patient is on medical therapy for relief of pain, any form of fertility enhancing treatment cannot be initiated. However, medical treatment as an adjunctive therapy (ultralong GnRH analogue) prior to ART has been advocated in advanced endometriosis in the absence of big endometriomas and adenomyosis with a view to enhance ART outcome.

While considering the management of sub-fertility in advanced endometriosis the place of expectant management with expectation of spontaneous pregnancy can be ruled out. Because women with advanced endometriosis will have significant pelvic structural abnormalities with extensive adhesions that may compromise the patency, mobility and function of the fallopian tubes and other reproductive organs.

The treatment and expected outcome in an advanced endometriosis have been outlined in following Table-4.

	Relief of symptoms	Disease volume	Improvement of fertility potential
Medical management	Effective	May or may not be effective	Not effective
Conservative surgery	Effective	Effective	Effective
Medical followed by surgery	More effective	More effective	More effective
ART alone	-	-	Not as effective as combination
ART preceded by surgery or GnRH-a	-	-	More effective

From the above table it is apparent that ART when preceded by surgical or medical treatment is the most effective approach for fertility restoration in advanced endometriosis. But the outcome of ART alone in advanced endometriosis is not very rewarding.

Why ART alone is not effective?

Because majority of women with advanced endometriosis will have a complex pelvic anatomy. The normal anatomy is disturbed by presence of chocolate cyst of variable sizes, nodules in Pouch of Douglas, moderate to severe pelvic adhesions, hydrosalpinx and unilateral or bilateral pseudocyst formed by adhesion amongst omentum, rectum, adnexal structures and uterus. These anatomical distortions without prior correction by medical or surgical treatment may adversely affect outcome of ART. The reasons for poor outcome are – (i) poor response to COS (ii) difficult accessibility of follicles during oocyte retrieval (iii) poor oocyte quality and (iv) sub-optimal endometrial receptivity. Surgical treatment through ablation, cauterization and resection reduces the volume of the disease and thereby prevents to some extent the adverse immunological impact on oocyte quality and endometrial receptivity. This is not possible when uterus is grossly enlarged or abnormally distorted because of adenomyosis or adenomyomas.

Types of pre-ART conservative surgeries

Usually three types of conservative surgeries have been advocated –

a) Surgeries for endometrioma – stripping/ resection when the cyst size is more than 4cm
b) Resection of recto-vaginal septum nodules with or without adhesiolysis
c) Only adhesiolysis – indicated in superficial (flimsy adhesion)or deep infiltrating (dense adhesion) endometriosis with or without myomectomy, adenomyomectomy, ovarian cystectomy etc.

(This is apart from surgical treatment of hydrosalpinges often associated with advanced endometriosis)

Surgeries for endometrioma:

Currently surgical treatment for endometrioma has become a controversial issue. Long-back surgery was indicated when size of endometrioma was more than 5cm. Subsequently the limitation of endometrioma size came down to 4cm. Very recently it has been debated that endometrioma surgery reduces ovarian 'reserve' and therefore unless there are strong indications like pain, very big size – surgery for endometrioma should be avoided specially when the surgery is being repeated for recurrent endometrioma. However, there are points in favour as well as point against pre-ART endometrioma surgery.

Points in favour –

- Pain
- Exclusion of malignancy
- To prevent problems during egg aspiration
    - o Ovarian infection –abscess –loss of the ovary
    - o Contamination of punctured follicles with endometriotic fluid: effect on quality?
    - o Inability to access all follicles
- Improving IVF outcome? – better COH response ?

Points against -

- Follicles (oocyte) are lower in number in operated ovaries16
- IVF responsiveness to COS
    - o the number of developing follicles reduced
    - o the number of oocytes retrieved reduced
- AMH decrease after surgery[17]

How does endometrioma surgery affect ovarian reserve?

Concern has been expressed over the risk of damaging ovarian reserve by surgically treating ovarian endometriomas.18 It is not very clear whether the damaging effect is likely to be more due to excision of the capsule or the use of electro-surgery. Ablation may carry higher risk of recurrence but there is concern that excision may result in greater damage to follicular reserve, which may compromise future ovarian response during IVF. The ureters may also be damaged by electro-cautery because they remain adherent to the endometriomas and therefore must be carefully identified before adhesiolysis or using electro-surgery. Meticulous haemostasis and use of adhesion preventing agents are advisable. ***Simple use of fenestration with drainage of endometrioma is not at all advisable because it carries a higher risk of recurrence.***

Summarizing all these facts, it may be suggested that surgery should be done cautiously and very judiciously. This is because surgery is associated with some concern about ovarian reserve as listed below.

- 25% fall in AMH for first OMA surgery19-endometrioma
- 60% fall in AMH after second surgery20
- B/L surgery has 60% reduction in AMH19
- 2% will have POF

However decrease in AMH level after surgery is influenced by – (a) surgical technique (b) age of the patient (c) depending on the surgery performed for unilateral or bilateral chocolate cyst.

What does the guideline say?

ESHRE guideline (2014)15 has outlined the following points for pre-ART surgery in endometrioma and pelvic adhesions in advanced endometriosis.

a) *Intelligent consideration is essential for ablation of endometriomas and adhesiolysis of pelvic adhesions to improve endometriosis associated pain and accessibility of follicles*

b) *However, decision should be considered carefully specially in women with history of previous ovarian surgery*

c) *It is not always correct to say that surgery is contraindicated in all cases*

d) *Now the question is how to make a decision?*

Decision making – The decision should be considered based on the presence or absence of following subjective symptoms and objective findings – (a) Excruciating pain (b) size of the cyst which may obscure accessibility of follicles during egg retrieval (c) previous ovarian surgery (d) associated hydrosalpinx.

Not only the cyst resection but 'debulking' of adhesion, i.e. adhesiolysis, resection of fibromyoma, adenomyoma may make her fit with possible positive outcome in terms of follicular responsiveness to COS, accessibility of follicles for oocyte retrieval and endometrial receptivity for blastocyst implantation.

But the primary requirement for an effective pre-ART surgical treatment is – 'experience and expertise of laparoscopic surgeon'. Special training for pre-ART conservative laparoscopic surgery for advanced endometriosis is urgently required. Therefore, for decision making it is essential to have a definite algorithm of infertility workup for advanced endometriosis.

If conservative surgery has been preferred with ovarian cystectomy how long to wait before ART is planned?

The planning should be done depending on age of the patient, size of the cyst and degree of adhesion. In young women if the size of the cyst is not very big and adhesions are moderate or minimum and the anatomical restoration of the pelvic organ has been reasonably accomplished by conservative surgery – a period of two years may be allowed either for spontaneous pregnancy to occur or may be helped with COH-IUI. But when these conditions are unfavourable even in young women, IVF should be planned within three months. In elderly women (age>37 yrs), IVF is the treatment of choice ***immediately*** following conservative surgery.

However in young women following conservative surgery, if IVF is not done immediately, , there is risk of reactivation or recurrence of the cyst if pregnancy does not occur within two years. Under such situation the subsequent plan consists of →

Ultralong GnRH-a
For 3-6 months → 2nd look laparoscope →
Excision Of Residuals Or Recurrence

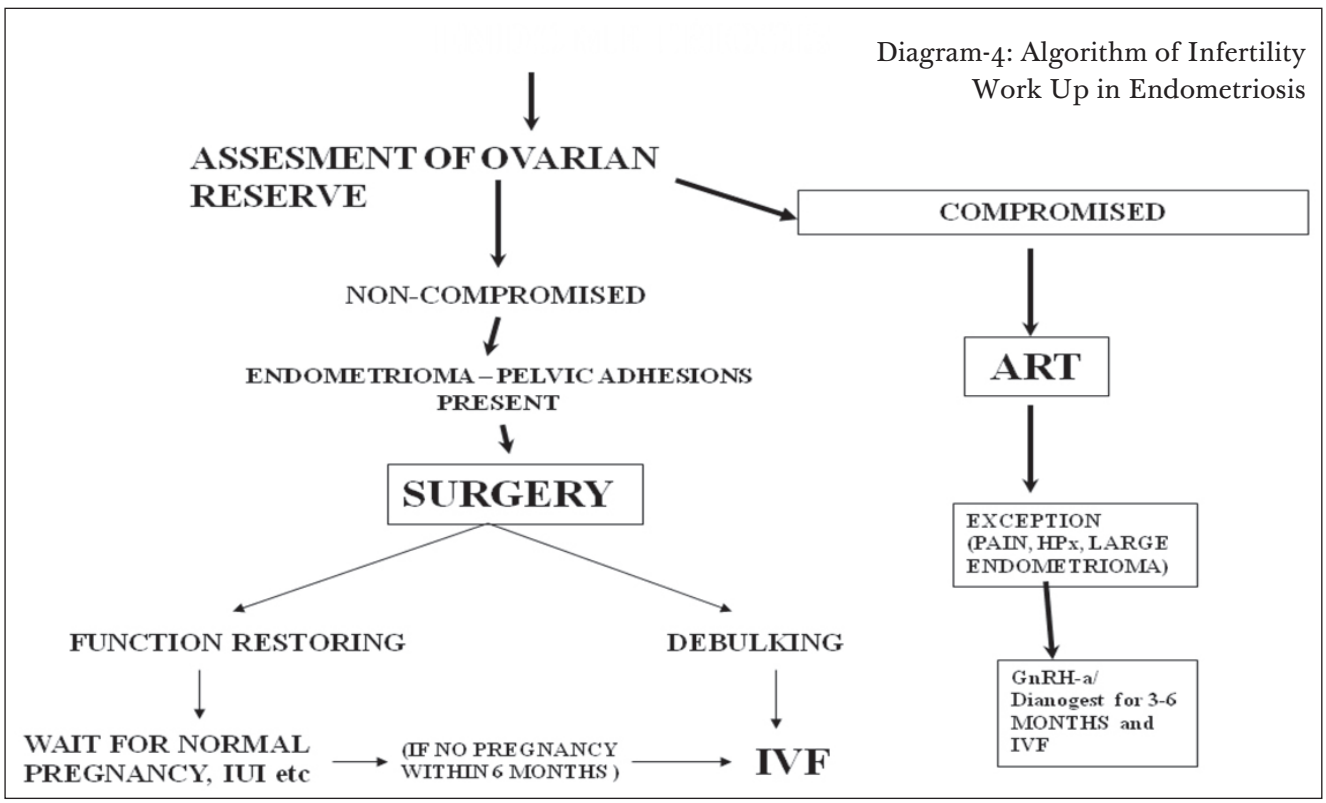
↓

IVF (NO FURTHER WAITING)

Resection of RV septum nodule and adhesiolysis:

The next pre-ART surgical procedure is resection of recto-vaginal septum nodule with or without adhesiolysis. The ESHRE guideline (2014)[15] has confirmed the effectiveness of surgical excision of deep nodular lesions of the rectovaginal septum and adhesiolysis before ART with regard to reproductive outcome.[21,22]

Diagram-4: Algorithm of Infertility Work Up in Endometriosis



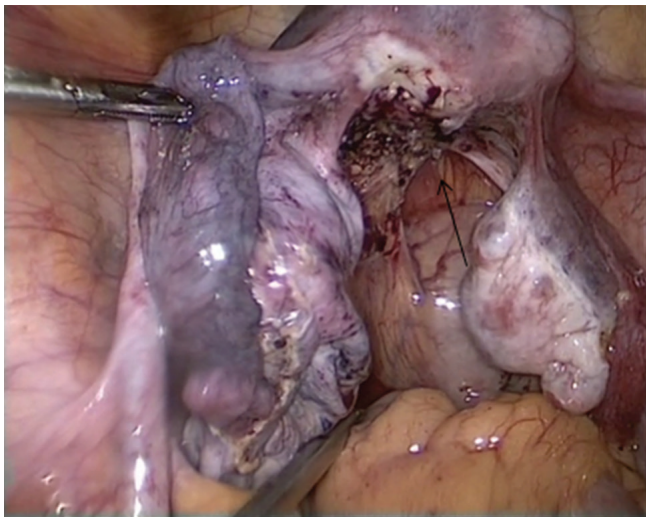


Diagram-5: Rectovaginal septum nodule infiltrating into rectovaginal space

However it must be emphasized that recto-vaginal septum nodule is a type of adenomyosis.

Even a few years back, adenomyosis and pelvic endometriosis were considered to be different disease entities. This concept is gradually changing because of better diagnostic methods of adenomyosis like 3D USG scan or MRI.

Prevalence of adenomyosis with endometriosis:

Older text books reported the association of adenomyosis with endometriosis is approximately 8 to 20%. Current few informations summarized below however indicate higher incidence of association –

- ***Kunz et al***, (2005)[23] reported association of adenomyosis of 79% with endometriosis and 28% without endometriosis
- Other observers[24] reported association with endometriosis of 52.5% and 8-20% without endometriosis
- Our incidence at IRM was : association of adenomyosis with endometriosis is 57.35% and incidence of adenomyosis without endometriosis is 14.5%

Most of these studies indicate a strong association between advanced endometriosis and adenomyosis. But even now, some believe that two conditions are different stages of the same disease, while others identify them as separate entities; one associated with infertility and the other associated with multi-parity.

RV nodule and uterine adenomyosis – ethnic variation

It is generally believed that uterine adenomyosis is more common in black women (Asian & African) where as adenomyosis of the rectovaginal septum is more frequent in Caucasian population (both are different varieties of adenomyosis). RV septum endometriosis originates from mullerian remnant in the rectovaginal tissues which grows downwards between rectum and vagina. Whereas in south east Asian women the mullerian tissue has a tendency to grow vertically upwards to produce uterine adenomyosis.

This variation of origin is therapeutically significant. RV septum nodules are surgically resectable whereas there is no effective conservative surgical treatment for uterine adenomyosis. Therefore our results of ART in advanced endometriosis with or without prior surgery are poor compared to those reported by authors of western countries.*(Table-4)

TABLE 5: shows difference in pregnancy outcome between our series compared to those reported by western authors:

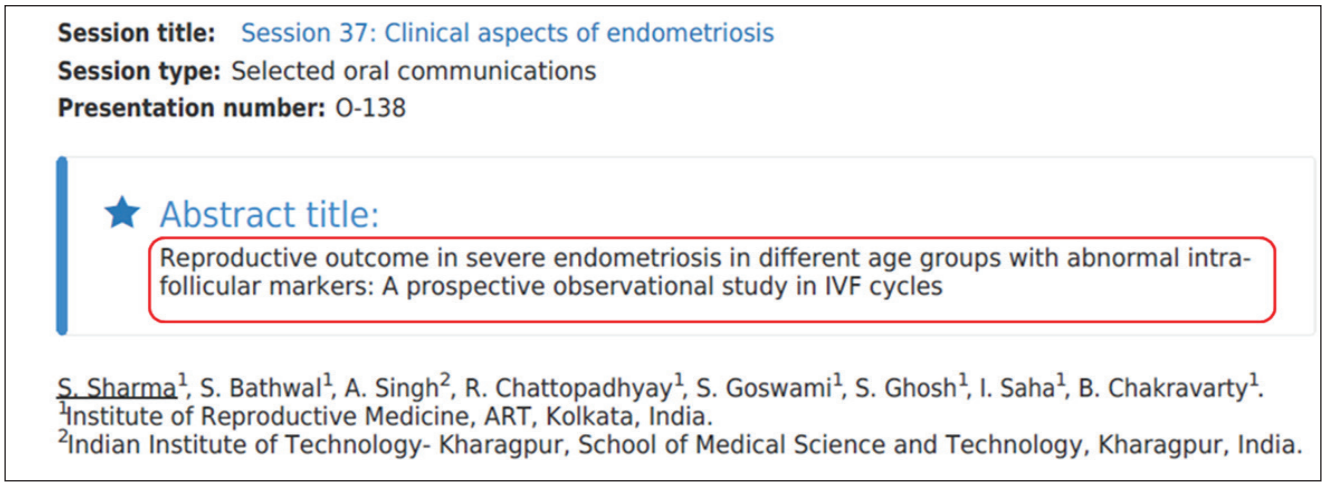
AUTHOR	MODERATE	SEVERE
OLIVE & LEE (LASER LAP-1996) (n=77)	22/43 (51.1%)	10/34 (29%)
OUR SERIES (2001-2004 BOTH LAPAROSCOPE & LAPAROTOMY) (n=74)	14/54 (25.93%)	2/20 (10%)

*Our results are poor - ? Association of adenomyosis more prevalent in 'Black' compared to 'white women'

Adhesiolysis (in infiltrating endometriosis):

In advanced endometriosis, in addition to the pathological lesions already described like endometrioma, RV nodule, adenomyosis, pelvic adhesions almost always coexist. Clinically two types of adhesions are encountered:

- ***Less adhesion*** – pre-ART surgical treatment consists of adhesiolysis,- restoration of anatomical proximity of tubes and ovaries, - this may be considered as 'function restoring surgery'. There is a fair scope of either spontaneous pregnancy or pregnancy following COH-IUI
- ***Dense adhesion*** – in these cases the conservative surgery performed are adhesiolysis, excision of endometrioma, fibromyoma, adenomyoma in order to make her fit for subsequent ART treatment. This is known as '*debulking surgery*'. This type of pre-ART surgery may be necessary



Session title: Session 37: Clinical aspects of endometriosis
Session type: Selected oral communications
Presentation number: O-138

Abstract title:

Reproductive outcome in severe endometriosis in different age groups with abnormal intra-follicular markers: A prospective observational study in IVF cycles

S. Sharma[1], S. Bathwal[1], A. Singh[2], R. Chattopadhyay[1], S. Goswami[1], S. Ghosh[1], I. Saha[1], B. Chakravarty[1].
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for the other phenotype, - 'frozen pelvis' - Outcome is very poor

Success rate after 'function restoring surgery':

One study suggests25 that following conservative surgery results were better after COH-IUI than no treatment when procedure involved -

- Adhesiolysis
- Endometriosis stripping/resection
- Distal tubal reconstruction according to the type of tubal lesion

Following these surgical procedures, results following COH-IUI were better than no treatment is shown in Table-6

	MODERATE
COH-IUI/IVF	46-56%
No Treatment (Results Following Surgery Only)	27%

- Limitations of conservative surgical treatment
- Ultralong GnRH-a followed by IVF }

[*These areas have already been covered in Vol.2, chapter 12 of this book.*]

Global opinion on ART in Endometriosis

The reports are conflicting. One group of workers26,27 reported that there is no specific adverse impact of advanced endometriosis on pregnancy outcome after ART. While several other studies reported adverse outcome of pregnancy following ART in advanced endometriosis as compared to women without endometriosis.

Counseling for endometriosis patient likely to take ART treatment

For counseling following points are significant –

- Slightly increased amount of medication is required; may be because of diminished ovarian reserve. Diminished ovarian reserve is not only for surgical resection of ovary for endometrioma but may also be due to loss of follicles due to disease itself.
- Cancellation rate may also be higher because of diminished stimulation response to COS
- Slightly decreased risk of hyperstimulation

Though decrease in chances of implantation, live birth, pregnancy rate are statistically significant – but our observation suggests that this may be related to age of the patient rather than extent of the disease. Our preliminary observation was presented in the ESHRE conference 2016.

This study suggested that –

'Younger women with severe endometriosis had similar reproductive outcome as tubal factor infertility irrespective of lower oocyte/embryo yield and abnormal intra-follicular cytokines/angiogenic factors – presumed to have bad quality oocytes'.

But in general, it is assumed that IVF pregnancy rate is still inferior compared to tubal factor infertility. The discrepancies may be because other published reports did not classify the results based on age of their patients

Why in general, it is still believed that pregnancy rate in IVF with endometriosis is inferior to those achieved in tubal infertility –

This may be because either oocyte or endometrium or both may be at fault (already discussed in detail in Volume-II, Chapter No.12 of this book).

Risk of endometriosis – related symptom progression following ART:

A possible concern has been raised about the risk of endometriosis associated symptom progression following ART. Because controlled ovarian hyper stimulation (COHS) leads to multiple follicular development accounting for considerable rise of serum oestradiol concentration. Endometriosis is an oestrogen dependant disease and multiple follicular development has been blamed to play a critical role in the formation of ovarian endometrioma.[28,29,30,31]

Based on this concept, few studies initially documented some cases of women with deep peritoneal endometriosis, who had significant progression of the disease following IVF.[32,33] But subsequent studies (both retrospective and prospective) conducted by Benaglia et al (2011)[31] inferred that IVF does not expose women to consistent risk of progression of endometriosis related symptoms. Further evidences are required particularly for specific group of women with deep peritoneal lesion.

Same option is also expressed by Santulli et al (2016)[34] These authors clearly expressed their views and concluded that assisted reproductive technology did not exacerbate the symptoms of endometriosis or negatively impact quality of life in women with endometriosis compared to disease – free women.[35]

Impact on pregnancy outcome in women with endometriosis who achieved pregnancy following treatment with IVF

It is well known that endometrium of women with endometriosis is functionally different from endometrium of healthy unaffected women. The differences exist at various levels:- Stem cell content, hormonal sensitivity, cellular proliferation, adhesion, invasiveness, angiogenesis and immune-modulation.[36,37] It is also becoming more reassuring that complications during 2nd and 3rd trimester of pregnancy, such as pregnancy induced hypertensive disorders or reduced foetal growth, may have their origin from local disturbances occurring at the time of implantation. Two recent systemic reviews[38] suggested that there is an increased risk of preterm birth and placenta praevia in pregnancies following ART in endometriosis compared to those in non-endometriotic group. But subsequently[39] based on their studies concluded that women with endometriosis do not face an increased risk of preterm birth. However, these women are more exposed to the risk of placenta praevia. But these authors also suggested that further evidence is required to confirm these intriguing associations.

Take Home Message

- ART improves reproductive outcome in all stages of endometriosis
- Judicious involvement of pre-IVF medical and surgical treatment in advanced endometriosis is almost always essential to improve the outcome
- Infertility in endometriosis is due to immune related dysfunction or disease related distortion or destruction of reproductive organs and their function
- Pregnancy outcome following ART treatment in endometriosis may be corelated in relation to extent of infiltration or invagination of endometriotic implant inside the pelvic tissue or organ
- Overall outcome of ART pregnancy rate in advanced endometriosis compared to the pregnancy rate in non-endometriotic women is not rewarding.
- Resection of endometriomas, pelvic nodules, cauterisation and ablation of endometriotic implants, adhesiolysis as pre-ART surgical procedure may help in improving ART outcome
- Currently resection of endometrioma as pre-ART procedure is a topic for debate
- Decision making depends on size, association of the pain, accessibility of follicles and history of previous ovarian surgery
- Removal of pelvic nodule and adhesiolysis will help to improve ART outcome in advanced endometriosis
- In deep infiltrating endometriosis and in some case of adenomyosis, ultra-long GnRH analogue followed by ART may help to

improve ART outcome

- Because of large amount of oestrogen release following multi follicular development after COH, there is an apprehension of progression of associated symptoms following ART procedures.. These views have not been substantiated through reports published so far.
- Except a marginal increase in the incidence of placenta preavia, no adverse pregnancy related outcome has been recorded in women with endometriosis achieving pregnancy following ART.

REFERENCES:

1. Guo SW, Wang Y. The prevalence of endometriosis in women with chronic pelvic pain. Gynecol Obstet Invest 2006;62:121–30. doi:10.1159/000093019
2. Brizek CL, Schlaff S, Pellegrini VA, Frank JB, Worrilow KC. Increased incidence of aberrant morphological phenotypes in human embryogenesis - an association with endometriosis. J Assist Reprod Genet 1995;12:106–12. doi:10.1007/BF02211378
3. Hill JA, Faris HM, Schiff I, Anderson DJ. Characterization of leukocyte subpopulations in the peritoneal fluid of women with endometriosis. Fertil Steril 1988;50:216–22.
4. Saito H, Seino T, Kaneko T, Nakahara K, Toya M, Kurachi H. Endometriosis and oocyte quality. Gynecol Obstet Invest 2002;53 Suppl 1:46–51. doi:10.1159/000049424
5. D'Hooghe TM, Debrock S, Hill JA, Meulemann C. Endometriosis and subfertility: is the relationship resolved? Semin Reprod Med 2003;21:243–54. doi:10.1055/s-2003-41330
6. Adamson DG, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. Fertil Steril 2010;94:1609–15. doi:10.1016/j.fertnstert.2009.09.035
7. Akande VA, Hunt LP, Cahill DJ, Jenkins JM. Differences in time to natural conception between women with unexplained infertility and infertile women with minor endometriosis. Hum Reprod 2004;19:96–103. doi:10.1093/humrep/deh045
8. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, et al; ESHRESpecial Interest Group for Endometriosis and Endometrium Guideline Development Group. ESHRE guideline for diagnosis and treatment of endometriosis. Hum Reprod 2005;20:2698–704. doi:10.1093/humrep/dei135
9. Mahutte N, Arici A. New advances in the understanding of endometriosis related infertility. J Reprod Immunol 2002;55:73–83. doi:10.1016/S0165-0378(01)00130-9
10. Practice Committee, ASRM, Endometriosis and infertility, Fertility and Sterility, Volume 82, Supplement 1,2004,Pages 40-45,
11. Pal L, Shifren JL, Isaacson KB, Chang Y, Leykin L, Toth TL. Impact of varying stages of endometriosis on the outcome of in vitro fertilization-embryo transfer. J Assist Reprod Genet 1998;15:27–31
12. Harlow CR, Cahill DJ, Maile LA, Talbot WM, Mears J, Wardle PG, et al. Reduced preovulatory granulosa cell steroidogenesis in women with endometriosis. J Clin Endocrinol Metab 1996;81:426–9.
13. Khamsi F, Yavas Y, Lacanna IC, Roberge S, Endman M, Wong JC. Exposure of human oocytes to endometrioma fluid does not alter fertilization or early embryo development. J Assist Reprod Genet 2001;18:106–9.
14. Pellicer A, Valbuena D, Bauset C, Albert C, Bonilla-Musoles F, Remohi J, et al. The follicular endocrine environment in stimulated cycles of women with endometriosis: steroid levels and embryo quality. Fertil Steril 1998;69:1135–41
15. G.A.J. Dunselman, N. Vermeulen, C. Becker, C. Calhaz-Jorge, T. D'Hooghe, B. De Bie, O. Heikinheimo, A.W. Horne, L. Kiesel, A. Nap, A. Prentice, E. Saridogan, D. Soriano, and W. Nelen. ESHRE guideline: management of women with endometriosis. Human Reproduction, Vol.29, No.3 pp. 400–412, 2014
16. Massimo Candiani, Maurizio Barbieri, Barbara Bottani, Carlo Bertulessi, Michele Vignali, Benedetta Agnoli, Edgardo Somigliana, and Mauro Busacca. Ovarian recovery after laparoscopic enucleation of ovarian cysts: Insights from echographic short-term postsurgical follow-up. Journal of Minimally Invasive Gynecology (2005) 12, 409-414
17. Hye Jin Chang, Sang Hoon Han, Jung Ryeol Lee, Byung Chul Jee, Byoung Ick Lee, Chang Suk Suh, and Seok Hyun Kim. Impact of laparoscopic cystectomy on ovarian reserve: serial changes of serum anti-Mullerian hormone levels. Fertility and Sterility_ Vol. 94, No. 1, June 2010
18. Lucena E, Cubillos J. Immune abnormalities in endometriosis compromising fertility in IVF-ET patients. J Reprod Med 1999;44:458–64.
19. Streuli I, de Ziegler D, Gayet V, Santulli P, Bijaoui G, de Mouzon J, Chapron C. In women with endometriosis anti-Müllerian hormone levels are decreased only in those with previous endometrioma surgery.Hum Reprod 2012; 27:3294–3303
20. Simone Ferrero, Carolina Scala, Annalisa Racca, Luana Calanni, Valentino Remorgida, Pier Luigi Venturini and Umberto Leone Roberti Maggiore. Second surgery for recurrent unilateral endometriomas and impact on ovarian reserve: a case-control study. Fertility and Sterility® Vol. 103, No. 5, May 2015.0015-0282
21. Bianchi PH, Pereira RM, Zanatta A, Alegretti JR, Motta EL, Serafini PC. Extensive excision of deep infiltrative endometriosis before in vitro fertilization significantly improves pregnancy rates. J Minim Invasive Gynecol 2009;16:174–180
22. Papaleo E, Ottolina J, Vigano P, Brigante C, Marsiglio E, De Michele F, Candiani M. Deep pelvic endometriosis negatively affects ovarian reserve and the number of oocytes retrieved for in vitro fertilization. Acta Obstet Gynecol Scand 2011;90:878–884
23. G.Kunz, D.Beil, P.Huppert, M.Noe, S.Kissler and G.Leyendecker. Adenomyosis in endometriosis prevalence and impact on fertility. Evidence from magnetic resonance

imaging. Human Reproduction Vol.20, No.8 pp. 2309–2316, 2005
24. S. Kissler, S. Zangos, J. Kohl, I. Wiegratz, A. Rody, R. Gätje, T.J. Vogl, G. Kunz, G. Leyendecker, M. Kaufmann. Duration of dysmenorrhoea and extent of adenomyosis visualised by magnetic resonance imaging. European Journal of Obstetrics and Gynecology and Reproductive Biology , Volume 137 , Issue 2 , 204 – 209
25. Karabacak O, Kambic R, Gursoy R, Ozeren S. Does ovulation induction affect the pregnancy rate after laparoscopic treatment of endometriosis? Int J Fertil Womens Med. 1999 Jan-Feb;44(1) 38-42. PMID: 10206198.
26. Matalliotakis IM, Cakmak H, Mahutte N, Fragouli Y, Arici A, Sakkas D. Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility. Fertil Steril. 2007 Dec;88(6):1568-72. Epub 2007 Mar 8.
27. Barbosa MA, Teixeira DM, Navarro PA, Ferriani RA, Nastri CO, Martins WP. Impact of endometriosis and its staging on assisted reproduction outcome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2014 Sep;44(3):261-78. doi: 10.1002/uog.13366. Epub 2014 Aug 13. Review.
28. Jain S, Dalton ME. Chocolate cysts from ovarian follicles. Fertil Steril 1999; 72:852–856
29. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Malspeis S, Willett WC, Hunter DJ. Reproductive history and endometriosis among premenopausal women. Obstet Gynecol 2004;104:965–974
30. Vercellini P, Somigliana E, Vigano P, De Matteis S, Barbara G, Fedele L. Post-operative endometriosis recurrence: a plea for prevention based on pathogenetic, epidemiological and clinical evidence. Reprod Biomed Online 2010; 21:259–265
31. Laura Benaglia, Edgardo Somigliana, Giulia Santi, Claudia Scarduelli, Guido Ragni, Luigi Fedele; IVF and endometriosis-related symptom progression: insights from a prospective study, Human Reproduction, Volume 26, Issue 9, 1 September 2011, Pages 2368–2372, https://doi.org/10.1093/humrep/der208
32. Renier M, Verheyden B, Termote L. An unusual coincidence of endometriosis and ovarian stimulation. Eur J Obstet Gynecol Reprod Biol 1995;63:187–189
33. Govaertis I, Devreker F, Delbaere A, Revelard P, Englert Y. Short-term medical complications of 1500 oocyte retrievals for in vitro fertilization and embryo transfer. Eur J Obstet Gynecol Reprod Biol 1998;77:239–243
34. P. Santulli, M.C. Lamau, L. Marcellin, V. Gayet, P. Marzouk, B. Borghese, Marie-Christine Lafay Pillet, C. Chapron; Endometriosis-related infertility: ovarian endometrioma per se is not associated with presentation for infertility, Human Reproduction, Volume 31, Issue 8, 1 August 2016, Pages 1765–1775, https://doi.org/10.1093/humrep/dew093
35. Pietro Santulli,Mathilde Bourdon, Marion Presse, Vanessa Gayet, Louis Marcellin, Caroline Prunet, Dominique de Ziegler and Charles Chapron. Endometriosis related infertility: assisted reproductive technology has no adverse impact on pain or quality-of-life scores. Fertility and Sterility® Vol. 105, No. 4, April 2016 0015-0282
36. May KE, Villar J, Kirtley S, Kennedy SH and Becker CM. Endometrial alterations in endometriosis: a systematic review of putative biomarkers. Hum Reprod Update 2011; 17:637–653.
37. Edgardo Somigliana, Paolo Vercellini, Paola Vigano, Laura Benaglia, Andrea Busnelli, Luigi Fedele. Postoperative Medical Therapy After Surgical Treatment of Endometriosis: From Adjuvant Therapy to Tertiary Prevention. Journal of Minimally Invasive Gynecology Volume 21, Issue 3, May–June 2014, Pages 328-334
38. Paola Vigano, Laura Corti, and Nicola Berlanda. Beyond infertility: obstetrical and postpartum complications associated with endometriosis and Adenomyosis. Fertility and Sterility® Vol. 104, No. 4, October 2015 0015-0282
39. Laura Benaglia, Giorgio Candotti, Enrico Papaleo,Luca Pagliardini, Marta Leonardi, Marco Reschini, Lavinia Quaranta, Maria Munaretto, Paola Viganò, Massimo Candiani, Paolo Vercellini and Edgardo Somigliana. Pregnancy outcome in women with endometriosis achieving pregnancy with IVF. Human Reproduction, Vol.31, No.12 pp. 2730–2736, 2016

Mullerian Anomalies;- A new Clinical Classification– Review and Report of few rare Anomalies

Dr. Baidyanath Chakravarty

Mullerian anomalies have been distinctly classified into two broad groups – (a) anomalies with presence of a functioning uterus and (b) anomalies with absence of functioning uterus (MRKH syndrome). Those with presence of a functioning uterus have been further subcategorized into three subgroups; - functioning uterus but with complete outflow obstruction, functioning uterus with partial outflow obstruction and functioning uterus with no outflow obstruction. Clinical presentation will vary depending on type of severity of defects. Similarly management complexities and their outcome have been outlined in relation to the severity or complexity of the existing anomalies. While making an overview of the different anomalies a few rare mullerian abnormalities have been presented and the outcomes of the treatment result in different groups and subgroups have been discussed.

Introduction:

Abnormalities of mullerian ducts may involve different segments of female genital tract either individually or collectively. In these women, phenotypes and external genitalia are typically feminine and gonads are histologically and functionally normal ovaries.

Disorders of mullerian duct development may adversely affect three distinct areas intimately involved in reproduction. The anatomical and physiological functions of reproduction which are closely related to development of mullerian ducts are:

(a) Cyclic menstruation
(b) Potential for reproduction
(c) Normal sexual function

This background allows us an opportunity to classify mullerian anomalies based on the broad subjective and objective findings, - with a view for planning the rational treatment protocol for specific group of anomalies.

For example, mullerian anomalies with presence of a functioning uterus will have a specific type of approach of treatment which is not similar to those applicable for mullerian anomalies with absence of a functioning uterus (MRKH). This is because Mullerian anomalies with a functioning uterus will have different sub-groups of abnormal anatomical presentation leading to total outflow obstruction (total cryptomenorrhoea), partial outflow obstruction (partial cryptomenorrhoea) or no outflow obstruction. The last group comprising normally menstruating women, may remain undiagnosed unless they have the subjective symptoms of infertility and/or recurrent pregnancy loss. Moreover, some of these anomalies are easily treatable while in others,- treatment may be extremely challenging.

Based on this concept, we have proposed a new therapeutic classification of mullerian anomalies with a view to categorize them in groups likely or unlikely to be benefited with available measures of surgical or semi surgical correction procedures.

Group A: Mullerian anomalies with absence of functioning uterus:- True amenorrhoea typical MRKH syndrome

Group B: Mullerian anomalies with presence of a functioning uterus but with –

- (B1) Complete outflow obstruction
- (B2) Partial outflow obstruction
- (B3) No outflow obstruction

Group C: Rare Mullerian anomalies; for example segmental absence of fallopian tubes; stenotic narrow introitus associated with either complete bladder (ectopia vesicae) or urethral exstrophy etc. (few case reports have been published by the author)

Anatomic and clinical presentation of these disorders:

GROUP-A: Mullerian anomalies with absence of functioning uterus;- Typical MRKH (Meyer Rokitansky Kuster Hauser Syndrome – True amenorrhoea)

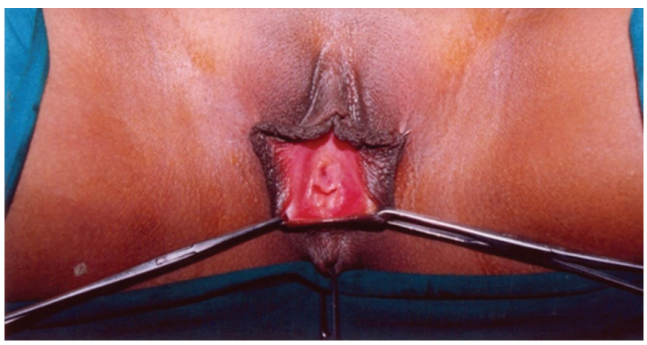
Incidence –

Literature survey provides a wide range of prevalence varying between 1 and 26%.[1] It has been reported that mullerian anomalies have a mean prevalence of 3-4%[2] worldwide. Of all mullerian anomalies, the incidence of MRKH syndrome has been reported to be varying between 1 in 4000 to 1 in 10000.[3] While some studies attribute gonadal dysgenesis and mullerian anomalies to be the two most common causes of primary amenorrhoea,[4,5] other reports specially from India[6] and Thailand[7] suggest MRKH syndrome to be the most common cause of primary amenorrhoea.

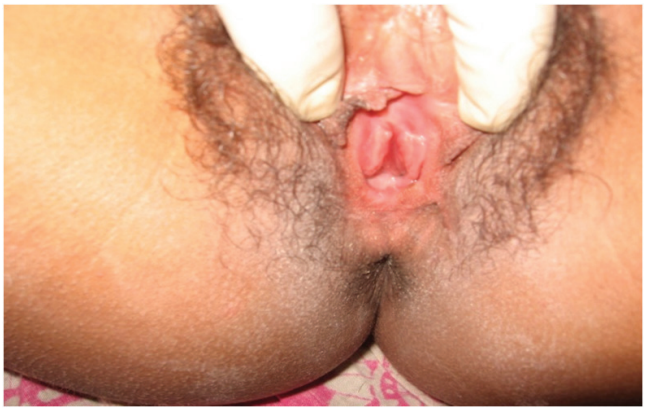
Clinical presentation:

They usually present during adolescence with symptoms of primary amenorrhoea and 'blind' vagina. Vagina may be absolutely blind or there may be a vaginal pouch (about 2.5cm depth). Reared up as females, they have typical female phenotype with normal development of breast, female body proportion, hair distribution, external genitalia and 46 XX chromosome. They may have associated skeletal and other abnormalities specially related to kidney, urethral opening and spine. Occasionally Turner's features may be associated with MRKH syndrome.

Some of the commonly observed features of external genitalia are presented in following photographs (Fig-1a, 1b,1c) –



1.a) Blind Vagina with normal feminine appearance in MRKH Syndrome (a small vaginal pouch is visible)



1.b) MRKH syndrome: appearance of external genitalia; Big urethral opening in the central part of introitus with blind vagina.

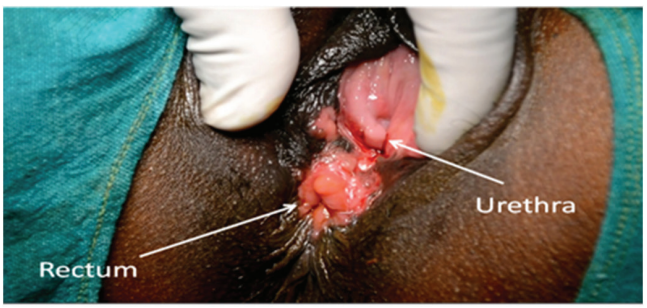


Fig- 1.c) This figure represents a case of blind vagina with absent introitus. The two big openings above and below the thin strip of perineal skin are the dilated urethra and dilated rectum. Photograph of external genital organ is from a married girl. She used to have satisfactory sexual relation either through rectal or urethral opening

Internal pelvic organs in MRKH syndrome:

Two solid mullerian bulbs (embryologic precursors of uterus) are seen on either side of the pelvis connected by a thick solid fibromuscular band running underneath the vesico-rectal fold of peritoneum just behind the bladder. The downward and medial-ward migrating two mullerian ducts unite in the midline behind the bladder. The small knob behind the bladder detected on ultrasound may sometimes be reported as a small hypoplastic uterus. Ovaries look normal often polycystic. Fallopian tubes appear normal with normal patency though occasionally they are hyoplastic and blocked. In less than 10% of cases a functioning uterus (often bicornuate) may exist with haematometra and haematosalpinx. Even when the knobs are non-functioning small islets of haematometra may lead to periodic pelvic pain. Association of Endometriosis and fibroid are not uncommon with MRKH syndrome.

A few photographs (both operative and schematic) of internal pelvic organs of MRKH Syndrome are presented below (Fig-2a,b,c)

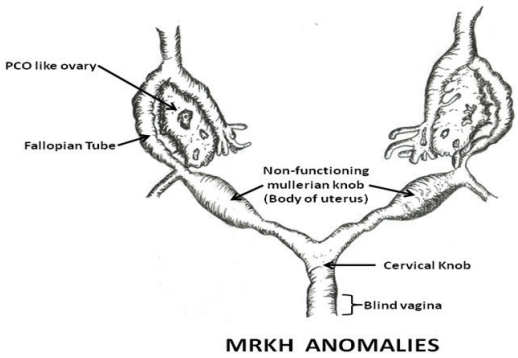


Fig-2a: Internal Pelvic Organs (Schematic)

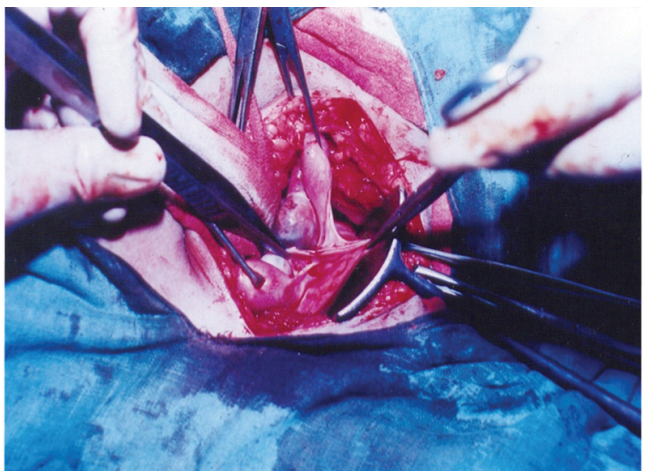


Fig-2b: Internal Pelvic Organs (laparotomy); MRKH- Bladder Peritoneum pulled up - cervical knob visible

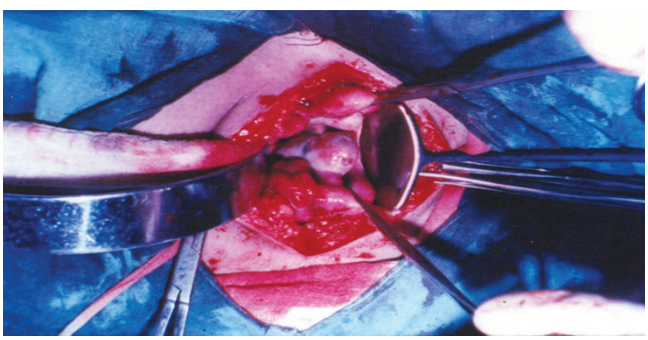


Fig-2c: Internal Pelvic Organs (Laparotomy); MRKH - Big Mullerian Knob, Big Ovaries (PCOS); Cervical knob behind the bladder is also seen. The mullerian knobs are also visible on either side of pelvis connected by a fibro muscular band running underneath the vesico-rectal fold of peritoneum

Diagnosis:

Clinical features, USG scan provide sufficient evidences for diagnosis. MRI may confirm but not mandatory and expensive as well.

Management of blind vagina (MRKH syndrome):

The treatment is to create a new vagina (neo-vaginoplasty) for restoration of sexual function. Menstrual and reproductive function cannot be restored. Surrogacy was the only choice for achieving a genetic motherhood. Recently, delivery of viable baby has been reported8 following uterine transplantation in women with MRKH syndrome. Even if uterine transplantation is possible in near future, vaginoplasty is pre-requisite for restoration of complete reproductive function.

Vaginoplasty:

There are two methods used for creating a new vagina – (a) non-surgical – pressure technique and (b) surgical – neovaginoplasty. Though majority of opinion is in favour of surgical correction, many gynaecologists including American Congress of Obstetrician and Gynaecologists have recommended non surgical pressure method as the first therapy since 2006.[9]

Various methods of creating a new vagina are listed below:

A) Non-surgical methods –

- **Dilatation**

Non-surgical method of creating of vagina by simple use of dilatation was first designed in 1938 by Frank and subsequently modified by Ingram.[10,11] (Fig-3)

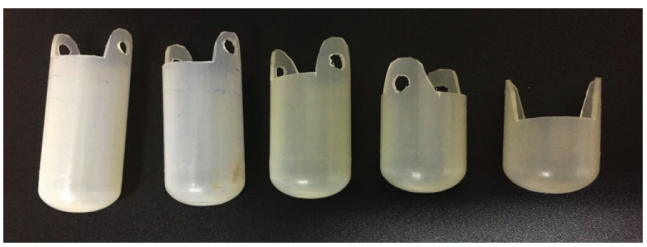


Fig-3: Vaginal moulds designed by author

Use of Moulds:

It has been reported that vagina formed by non-surgical pressure method remained permanent in depth and caliber even if the patient has neglected the procedure for more than a year.

Though success has been achieved following non-surgical method using Frank's or Ingram's technique but consensus of opinion is more in favour of surgical canalization of a blind vagina. If properly and

correctly performed it provides satisfactory results both anatomically and functionally.

B) Surgical Methods

Three Broad principles of currently used surgical methods (vaginoplasty):

a) Creation of a space between bladder and rectum. Dissection of an avascular space upto the peritoneum of POD is the primary step of a successful vaginoplasty.

b) A graft is essential to cover the raw area of the newly dissected space – commonly used for graft is split thickness autologous skin graft obtained from buttocks of the patient. Other types of graft have also been used (e.g. peritoneum, amnion, bowel etc)

c) 3rd and the most important step is to prevent constriction and closure of the space during the process of healing. This is achieved by continuous and prolonged dilatation by use of mould for a variable period of time during the post-operative phase.

The idea of modern vaginoplasty started following combined effort of Abbe – Wharton and McIndoe.[12,13,14] Primarily Abbe-Wharton showed the way by creating a space between bladder and rectum, necessity of placing an inlay graft and in addition, importance of continuous prolonged dilatation of the dissected space by placing a 'balsa form' during the contractile phase of healing.

McIndoe only popularized the method by giving it a substantial trial. The work was published in late 1940s.

Types of Vaginoplasty:

- Abbe McIndoe method(1938)12,13: inner wall of the cavity is lined with split thickness skin graft held in place with mould/forms
- Wharton(1938)14: placed a condom-covered mould instead of skin graft in the neovagina
- Different modifications of McIndoe (using different types of graft):
  - Full thickness skin graft
  - Amnion15,16
  - Peritoneum17
  - Interceed
  - Bowel vaginoplasty – Ileum,[18] Sigmoid.[19,20] Now these methods are obsolete. Occasionally these techniques are performed for vaginal augmentation or creation of vaginal pouch after exenteration operation.

Recent laparoscopic approach:

Only the basic approach of some of the commonly used procedures are being enumerated.

- **Vecchietti approach**[21]: vaginal dilatation with ovoid bead or mould in contact with vestibular area and attached to the abdominal wall by wires which are threaded retroperitoneally via laparoscope. Vesico-rectal space may or may not be dissected for negotiation of the wire. There is a risk of bladder and/or rectal injury by this procedure. (Fig-4)

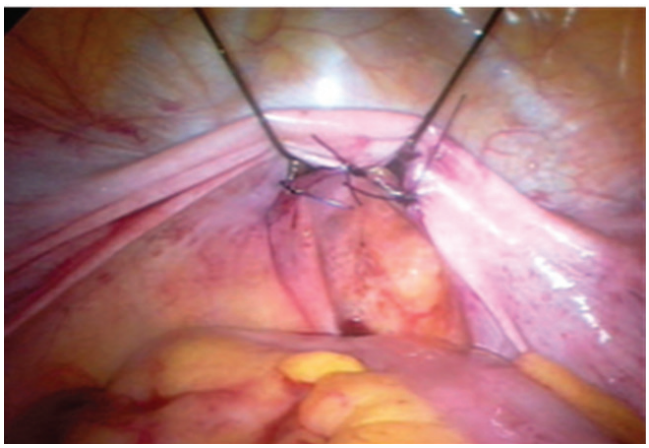


Fig-4: Laparoscopic Vecchietti Procedure

- **Davydov's Abdomino** (laparoscope) perineal approach[22]: Creating neovagina (by perineal dissection) and laparoscopic approach for dissection and fixation of peritoneal graft (through combined abdomino (laparoscope) perineal approach) and fixing peritoneal graft over the raw area of neovagina.

Differential diagnosis of absence of vaginal opening (blind vagina)

An anxious mother may bring her girl child before puberty when vaginal opening is not clearly visible (confusion with blind vagina). The causes of such abnormality in the child be be - (a) Labial adhesion, - due to low grade chronic valvitis (b) Labial fusion, - may be due to congenital adrenal hyperplasia

(CAH) or incomplete variety of testicular feminizing syndrome (c) imperforate hymen or (d) complete absence of vagina.

Clinical markers, USG scan, laparoscope, MRI, RIA and chromosomal analysis may identify the exact diagnosis. Previously, the provisional diagnosis was made by clinical landmarks including external examination which was corroborated by subsequent laparotomy. The approach to clinical diagnosis for differentiation of these defects have been presented in the following table format and photographic presentations.

	Imperforate hymen	Complete absence of vagina
Colour of the obstructing membrane	Pearly white, smooth	Pinkish with rogosity of obstructing membrane
Concavity or convexity of the obstructing membrane	Convex outwards	Concave inwards
Syringing and needle puncture test	Saline introduced through obstructing membrane can be reaspirated Microscopic examination reveals squamous epithelium	Saline injected cannot be aspirated
Rectal examination	Uterus palpable	Uterus not palpable

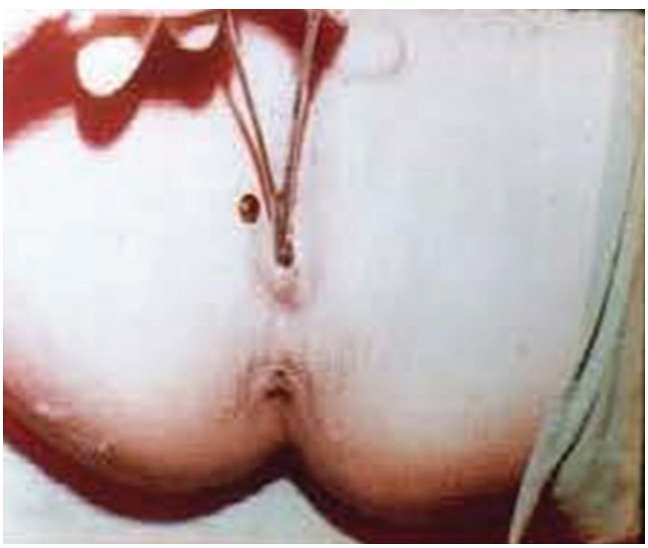


Fig 5a: Labial Adhersion

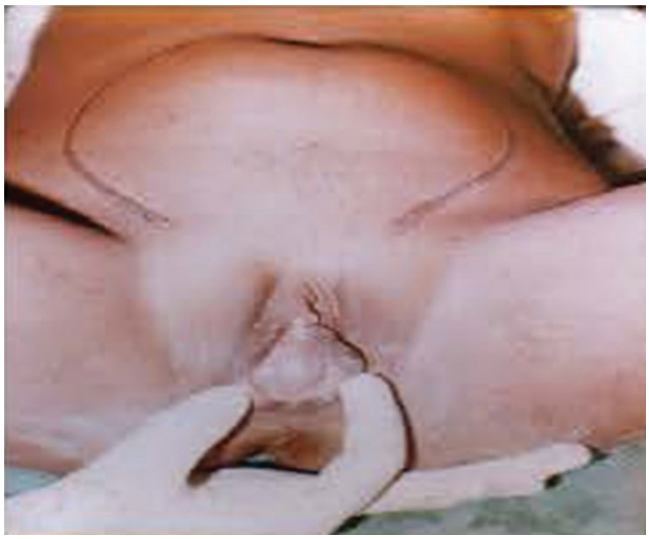


Fig 5b: Imperforate Hymen

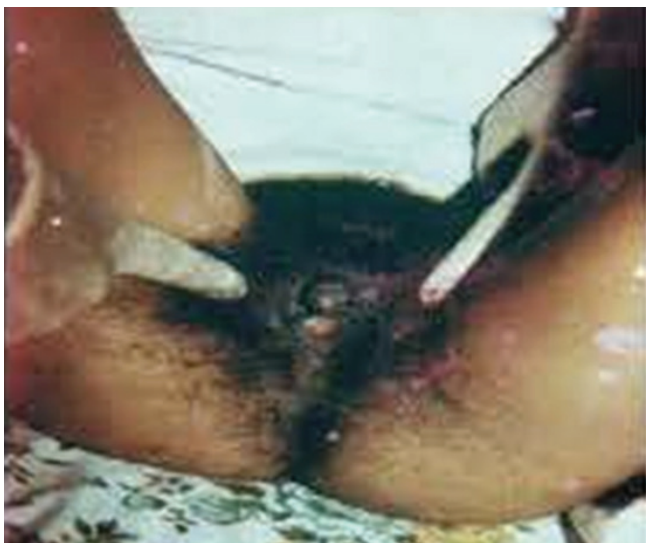


Fig 5c: Congenital adrenal Hyperplasia (Girl aged 14 years)

Fig 5d: Incomplete variety of Testicular feminizing syndrome in girl aged 12 year (absence of pubic hair)

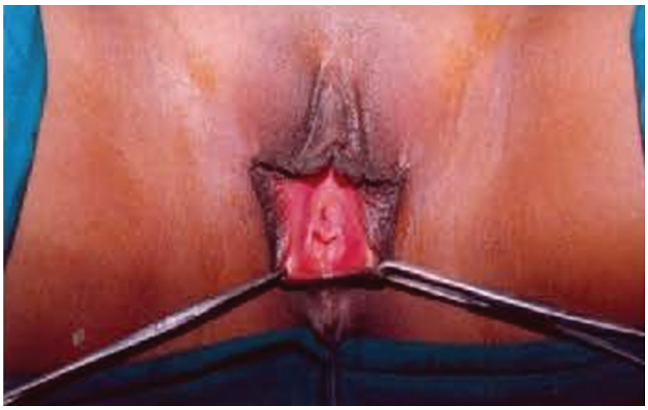


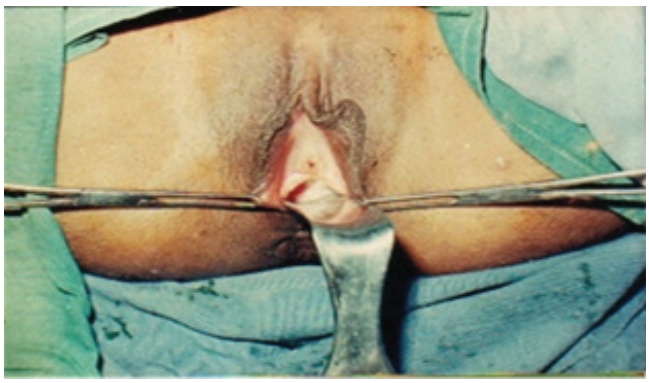
Fig 5e: MRKH - obstructing membrane - concave inwards, pinkish in colour rugosity +

Group B: Mullerian anomalies with a functioning uterus

Group B1: Mullerian anomalies with a functioning uterus but with complete outflow obstruction

Women with this group of anomaly may have three subtypes of defect with a normally functioning uterus – (a) cervical atresia (b) vaginal atresia and (c) cervico-vaginal atresia. Internal pelvic organ are normal and sometimes malformed (bicornuate and unicornuate) (Fig-6a & b). These patients present with primary amenorrhoea (cryptomenorrhoea) during adolescence. If they are not treated correctly and rationally during adolescence, their fertility potential will be lost. They exhibit obstructions at different levels of genital tract offering different grades of treatment complexities during surgical correction. Obstruction may be segmental or total, and usually involve either vagina, cervix or both. Segmental or total obstructive partition may exist at various levels of vagina, cervix or both (Fig-9a,b,c,d,e,f).

Mullerian Annomalies with Functioning Tuerus: Complete outflow obstruction - Haematometra with or without Haematocolpos



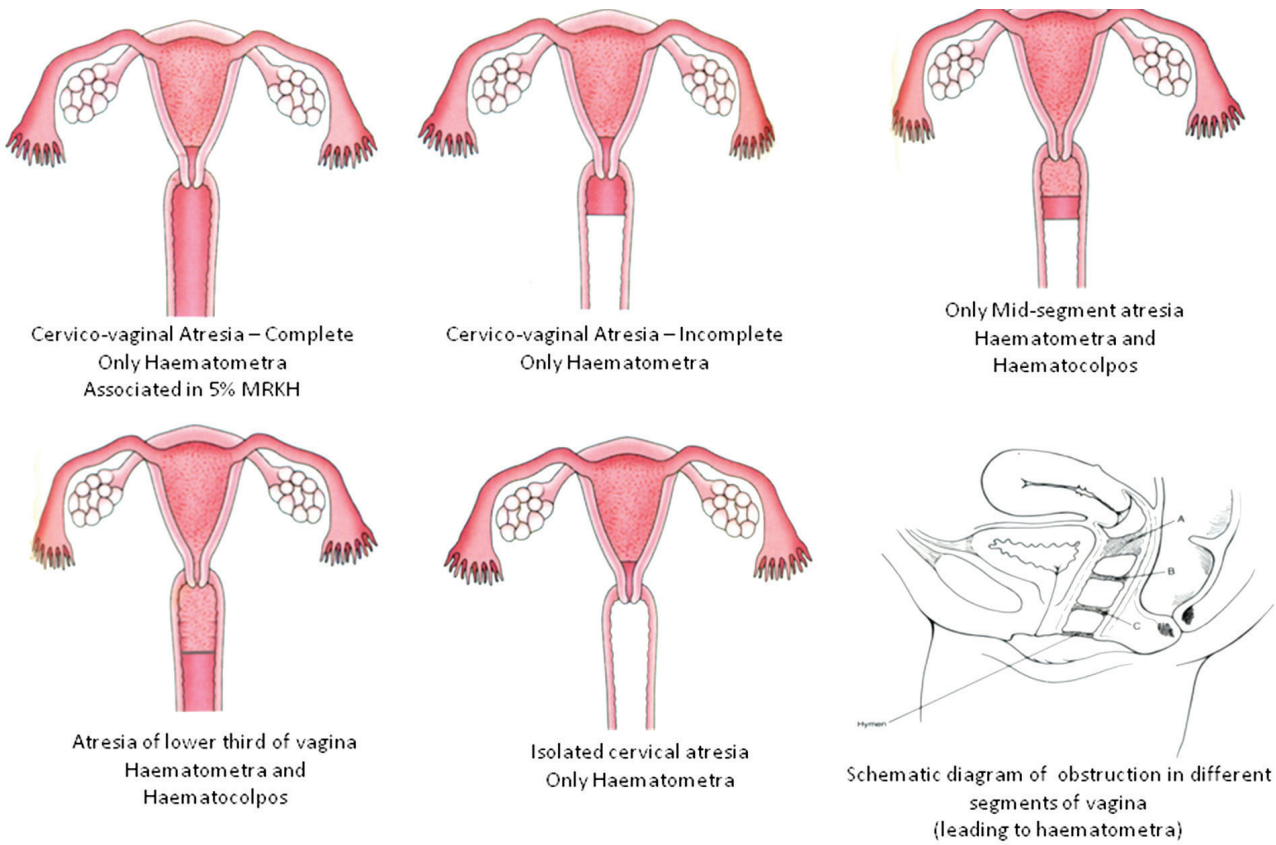


Fig-7a,b,c,d,e,f: Level of obstruction and operation complexities:

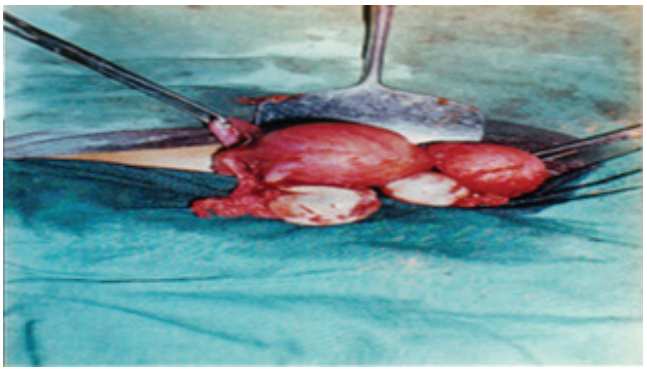


Fig 6a: Clinical Photograph

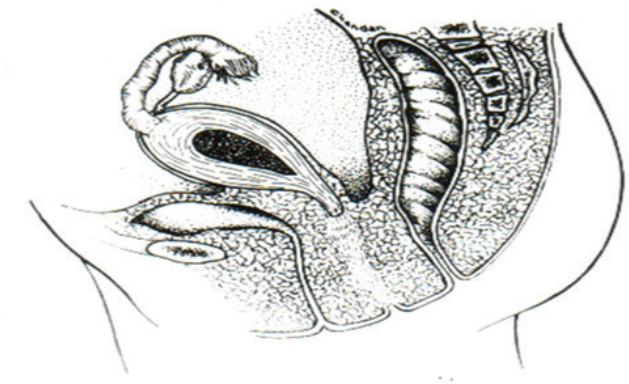


Fig 6b: Clinical photograph with Schematic Diagram

Operative complexities:

(a) Complete cervico-vaginal atresia – may be found in 5-10% of MRKH syndrome – only haematometra with or without haematosalpinx may exist (Fig-7a); operative difficulty – most complex

(b) Upto 1/3rd of vaginal atresia with complete/ incomplete cervical atresia may co-exist – only haematometra with or without haematosalpinx may co-exist(Fig-7b); operative difficulty – complex

(c) Midsegment vaginal atresia – haematometra and haematocolpos may exist together. (Fig-7c); operative difficulty – less complex than a & b

(d) Lower 1/3rd vaginal atresia without cervical atresia – leading to haematometra and haematocolpos (Fig-7d); operative difficulty – least complex

(e) Isolated cervical atresia – haematometra is present (Fig-7e); operative difficulty – complex but less than a & b

(f) Isolated transverse septum at various levels of lower genital tract (cervix and vagina) leading either to haematometra or to haematocolpos (Fig-7f)

The approach is abdomino-perineal/vaginal (except perhaps in Group-d) – currently laparoscopy is being used, previously laparotomy was the only choice

The levels of existence of transverse septum at different level of lower genital tract leading to total outflow obstruction has a significant impact on outcome of therapeutic intervention. With higher level obstruction, the success following recanalization is likely to be inferior than those with lower level of obstruction. Obstruction at the cervical level (cervical atresia) with or without vaginal malformation carries the worst prognosis following recanalization.

Cervical atresia:

Either only cervical or combined cervico vaginal atresia may be encountered in clinical practice. Both are difficult to be corrected. However, only vaginal rather than cervico-vaginal atresia is relatively easier.

There are two broad groups of cervical atresia – total and partial

Total cervical atresia:

Total absence of cervix is very rare, partial atresia is more common. In total atresia, corpus containing haematometra narrows down to a peritoneal fold to be connected with vaginal vault. Torsion of the corpus containing haematometra may occur with such abnormality.

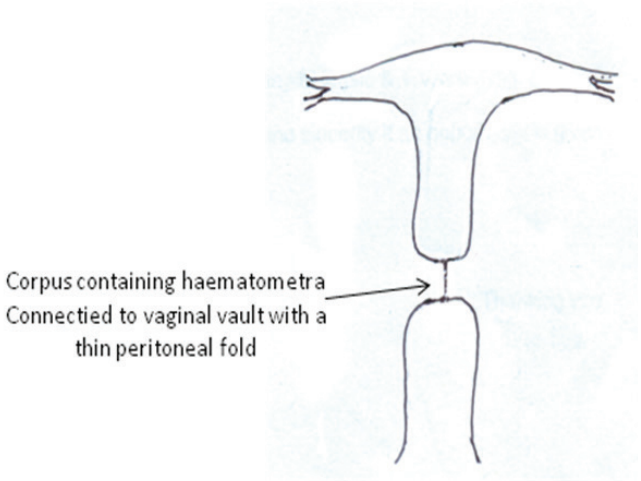


Fig-8: Total Cervical Atresia

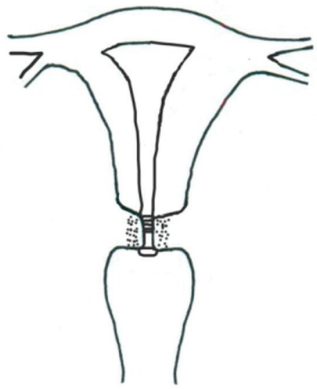


Fig 9a: Upper cervical atresia

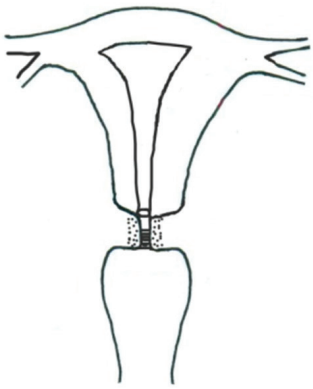


Fig 9b: Lower cervical atresia

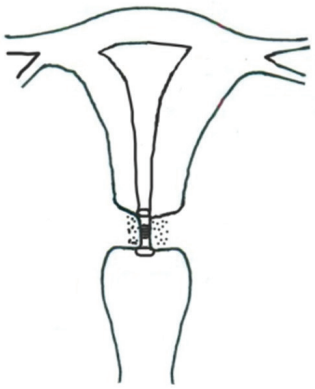


Fig 9c: Stenosis around center of cervix

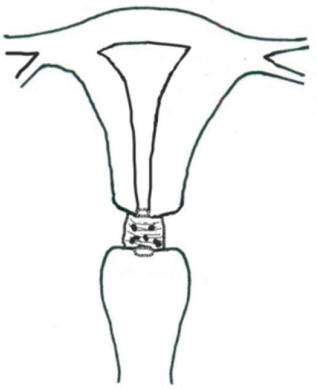


Fig 9d: Total stenosis of cervix

Partial cervical atresia:

The second variety, called partial cervical atresia may be sub-classified into four groups –

(a) Upper 2/3rd cervical atresia (Fig-9a)
(b) Lower 1/3rd cervical atresia (Fig-9b)
(c) Stenosis/constriction around center of cervix (Fig-9c)
(d) Total stenosis (but not absent) of cervix – cervical fragments encountered – occasionally on histology, cervical glands are seen (Fig-9d)

Clinical presentation:

These patients also present during adolescence with primary amenorrhoea (cryptomenorrhoea). Diagnosis is based on clinical features, USG and MRI. Exact site and extent of obstruction cannot always be precisely identified.

Treatment options (Group-B1):

There are two treatment options –

(a) Vaginoplasty or cervico-vaginoplasty with surgical canalization. This is also known as 'function restoring surgery'. If properly performed, adverse effects of retrograde menstrual blood flow following cryptomenorrhoea may be prevented.

However, there may be three objections against function restoring surgery (conservative surgery)–

a) Risk of restenosis
b) Endometriosis is not uncommon in these women
c) Absence of cervical epithelium and glands in cervical atresia compromising chances of pregnancy.

The selection criteria for surgical canalization are –

a) Age 12-20 years
b) No endometriosis
c) Not more than one previous attempt of surgical canalization is acceptable for repeat surgery

Surgical canalization either cervical or cervico-vaginal atresia has been attempted since 1980s. Previously this was performed through abdomino-perineal approach. Since 1990s, laparoscope has been introduced for surgical correction of cervical and cervico-vaginal atresia.

Restenosis and recurrence of outflow obstruction is the commonest problem which spoils this entire effort. This is common with cervical and cervico-vaginal atresia when compared with only vaginal atresia with a functioning uterus.

Various techniques and their modifications have been suggested to prevent restenosis. Some of them are mentioned below:

i) Kriplani 23 attributes use of a silicone stent in the neocervix until the resolution of inflammation is complete which was the main reason for reduction of restenosis in their cases.
ii) We have reported24 two stage procedure (vaginoplasty followed by cervicoplasty) through laparoscopic procedure and thereafter covering raw area of neo-cervix with vaginal flap – the same way as we cover raw areas following ampulation of cervix with Bonney's stitches

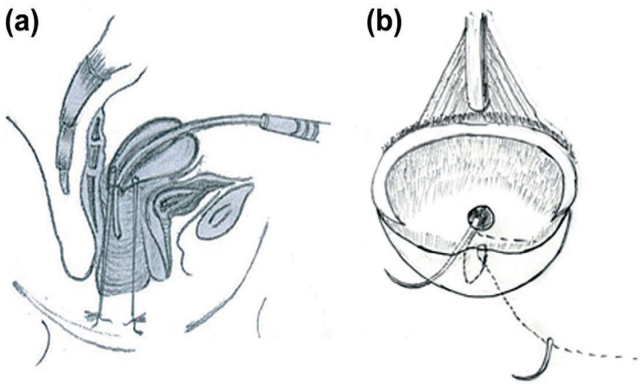


Fig-10a,b

iii) Acien25 described a more complicated procedure of excision of atretic area of cervix and reanastomosis of uterine corpus with neovagina

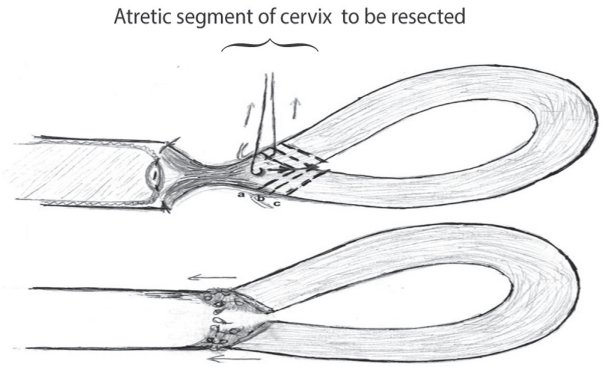


Fig-11: Vagino-corporeal reanastomosis

Apart from these technologies – the basic points which influence or help to prevent restenosis are the following – (a) size of channel (neocervix) (b) duration of stenting the channel (c) presence of a natural vagina adjacent to newly created channel and more importantly the ***number of menses occurring before the stent is taken out or displaced***.

Out of 28 cases treated and reported by us26 we achieved 2 viable pregnancies delivered by casarean section in cervioc-vaginal atresia (total vaginal & total cervical)

Group B2: Mullerian anomalies with presence of a functioning uterus with partial outflow obstruction

In this group, **one mullerian duct** is normally developed and canalized resulting in normal menstrual outflow, adequate potential for reproduction and usually no problem with sexual function.

Whereas, the **contra-lateral mullerian duct** though partially developed and functioning as a normal uterine horn with non-dissolution or partial dissolution of the partition formed by fusion of two mullerian ducts or failure of vertical fusion or non-canalisation with urogenital sinus will lead to following types of anatomical and clinical disorders.

Anatomical defect:- obstruction at the junction of upper 1/3rd and lower 2/3rd of vagina → clinical consequence – haematocolpos, haematometra, haemaosalpinx (Fig-12a)

a) **Anatomic disorder:** obstruction at the level of cervix → clinical consequence – haematometra and haematosalpinx (Fig-12b)

b) **Anatomic defect:** obstruction at the level of upper 2/3rd and lower 1/3rd of vagina. There may or may not exist a communicating channel between the two upper horn but collected blood of haematometra does not drain out completely unless the communicating gap is sufficiently big (Fig-12c). Clinical Consequences – haematometra and haematocolpos

c) **Anatomical defect:** a rudimentary mullerian knob pedunculated or sometimes sessile attached to normally developed and normally functioning mullerian horn. (Fig-12d & e). Clinical consequence – The rudimentary horn may be solid or canalized – containing haematometra when canalized. In pedunculated rudimentary horn the connecting stalk is usually not canalized & solid but occasionally may be canalized. Even with noncanalised stalk of functioning rudimentary horn ectopic pregnancy has been reported. Transperitoneal migration of spermatozoa may explain such type of unusual abnormal pregnancy. Rupture of horn due to ectopic pregnancy may sometimes be life threatening.

Clinical consequences of a rudimentary mullerian horn are –

- Haematometra
- Ectopic (cornual pregnancy)
- Torsion
- Impaction (in the pelvis) during labour (when rudimentary mullerian knob remains unrecognized)

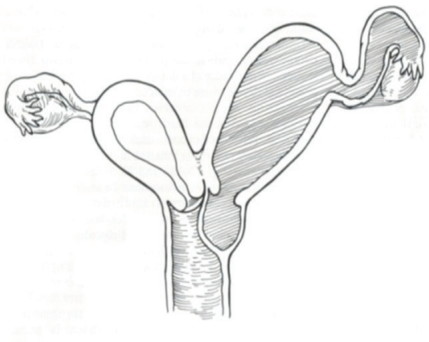


Fig-12(a): Partial obstruction at the junction of upper 1/3rd & lower 2/3rd of vagina

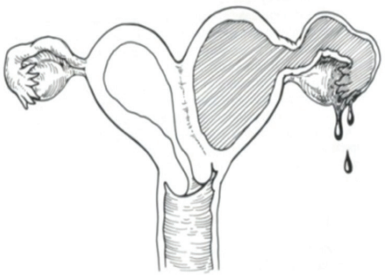


Fig-12(b): Partial obstruction at the level of cervix

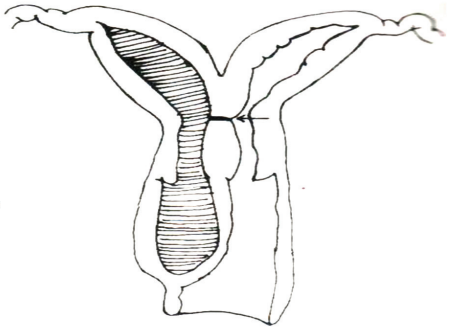


Fig-12(c): Partial obstruction at the level of upper 2/3rd & lower 1/3rd of vagina. There may exist a communicating channel at the level of cervix or lower part of body – may be insufficient in diameter for complete drainage of haematometra

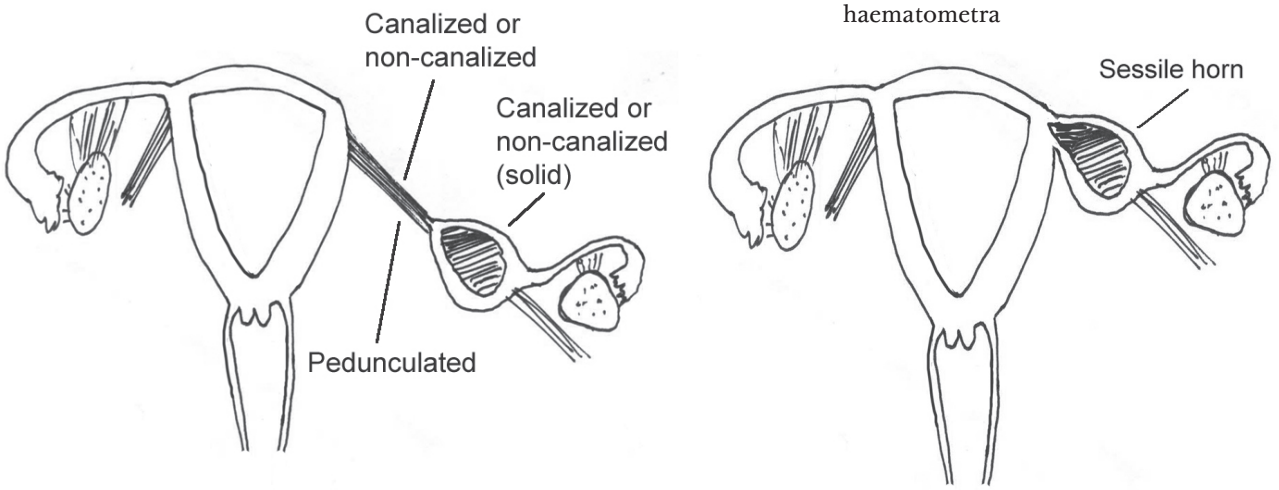


Fig-12(d & e): Rudimentary mullerian knob pedunculated or sometimes sessile attached to normally developed and normally functioning mullerian horn (well developed contra lateral horn uterus)

Management :

Excision of the obstructed segment, if properly performed at the correct age may restore all functions essential for reproduction. Presence of haematocolpos (low level obstruction) may create problem during surgical correction.

Group B3: Mullerian anomalies with functioning uterus but with no outflow obstruction

This may be the commonest non-symptom producing mullerian anomaly (seen in clinical practice). Anatomical variations of this group have been demonstrated in the following diagrams (Fig-13). Often these mullerian anomalies are diagnosed during routine investigation of infertility and recurrent miscarriage. Septate and subseptate uterus sometimes may have to be corrected by septoplasty. Cervical cerclage is an alternate and effective procedure for treating women with history of recurrent miscarriage associated with these mullerian anomalies. Unification of uterus didelphys or bicornuate uterus are rarely performed now-a-days. Uterine cavity augmentation by lateral metroplasty in unicornuate uterus though often suggested and reported to be a satisfactory procedure for the treatment of infertility and recurrent miscarriage has still remained controversial.

Rare mullerian anomalies

Two groups of rare mullerian anomalies have been reported by us:-

The first group (Group-a) consisted of two similar cases but with gross different anatomical presentation.[27]

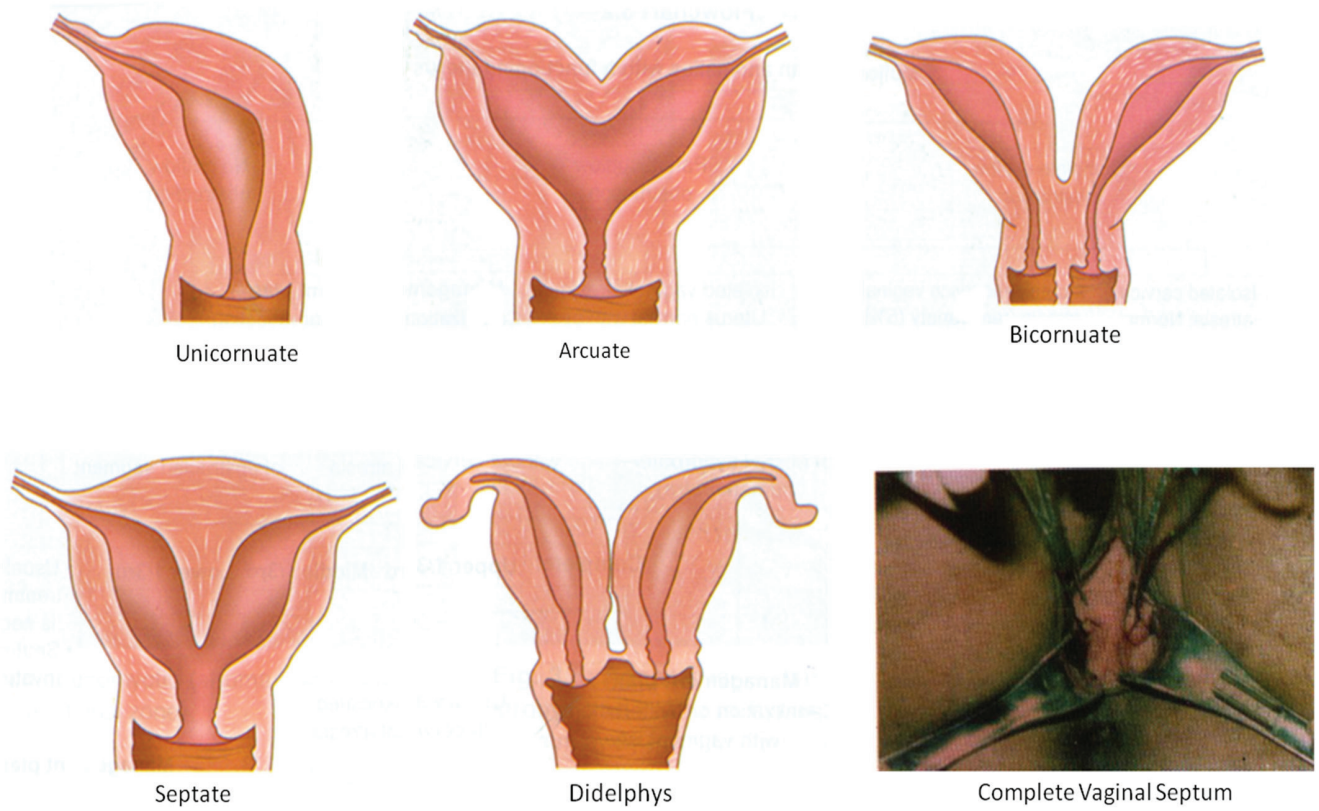


Fig-13: Types of mullerian anomalies

First case (Group-a1) – 17 year old girl had history of repair of anterior abdominal wall with autologous skin graft with colonic transplantation of ureters in childhood. On examination she had divergent labia, mons pubis, pubic rami and bifid clitoris. In addition the introitus was stenotic and was displaced in the region of mons pubis. She had normal menarche, normal menstrual cycle and no electrolyte imbalance as a consequence of uretero-colic anastomosis (Fig-14a,b)

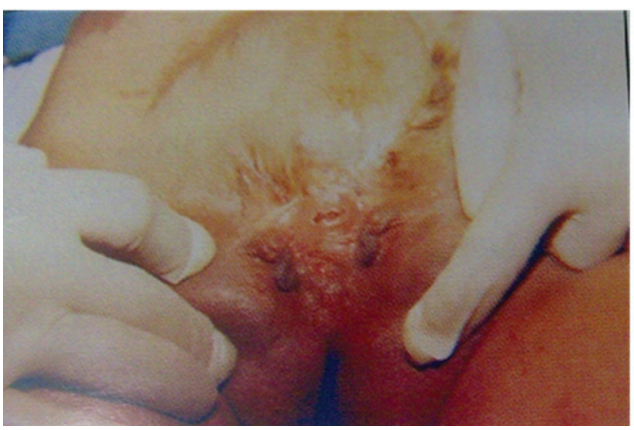
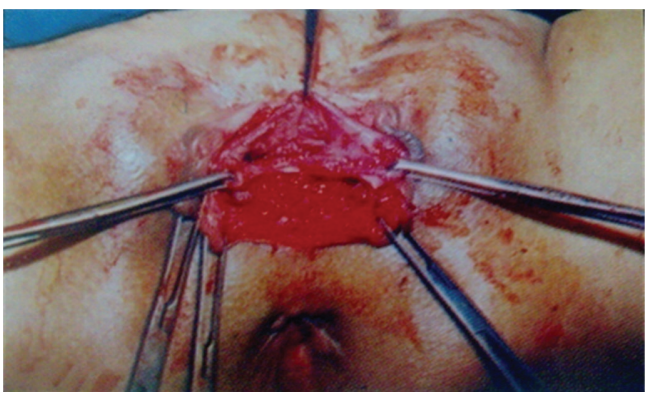
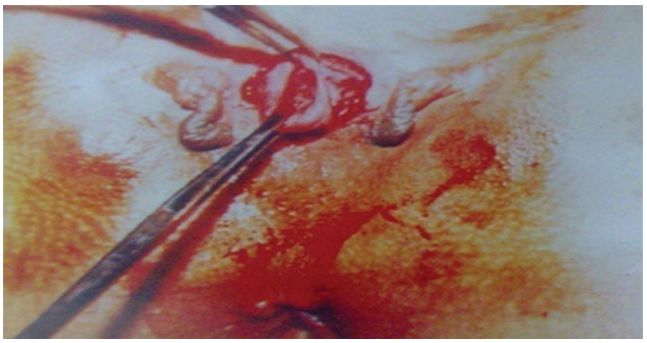


Fig-14a: Step-1- Group-a1 (Appearance of External Genitalia)

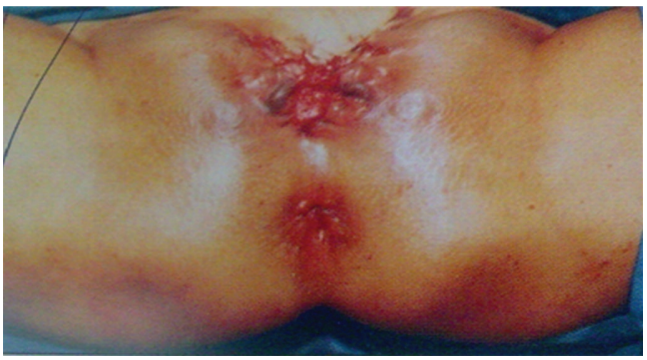
Second case (Group-a2) in the same group was a 19 year old girl with minimal grades of urethral exstrophy, with similar types of displaced stenotic introitus with divergent labia, Mons pubis and pubic rami. She had intact abdominal wall skin but with totally deficient abdominal muscles. She had no history of previous surgery and was having normal menstrual cycle. (Fig-15a,b,c)



Division of Perineum



Dissection of Vatinal Tube



Fixation of Disseced Vagina

Fig-14b: Step-2- Group-a1

Both of them had surgical reconstruction with introitoplasty and replacement of vagina in the perineal region. Both delivered viable babies within one year of surgery.

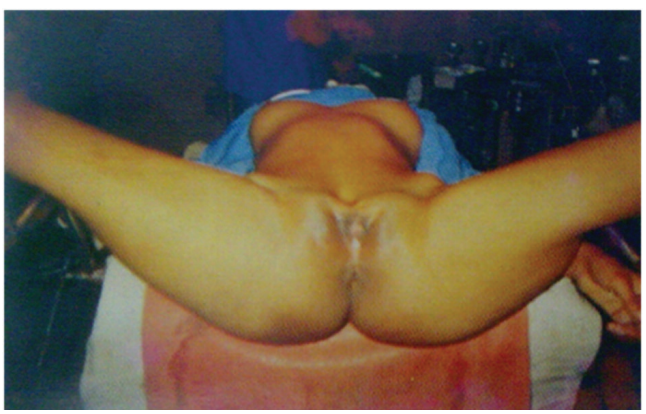
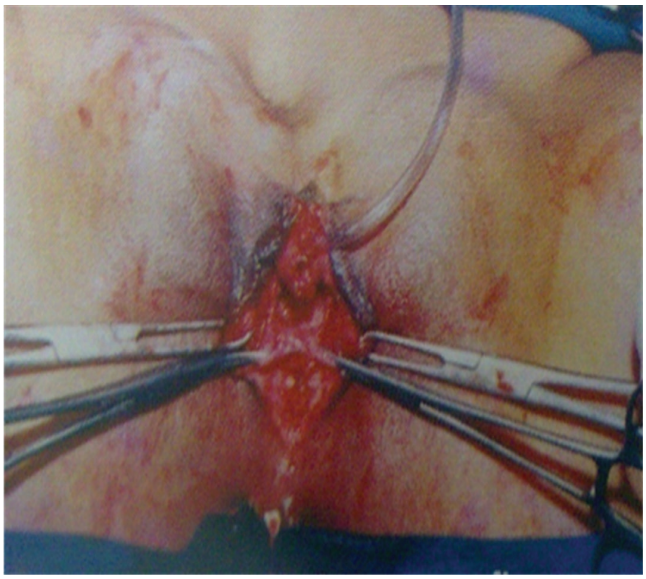
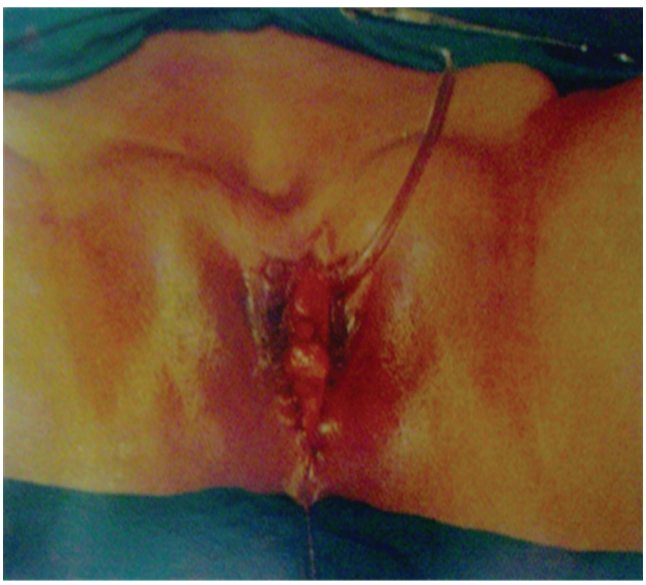


Fig-15b: Step-1- Group-a2. Appearance of External Genitalia, Scaphoid Abdominal Wall



Vaginal Tube Dissected, Perineum Dissected



Vaginal Mucosa fixed to Perineal Skin

Fig-15b,c: Step-2 & 3- Group-a2

In the second group (Group-b), 3 cases of isolated congenital tubal defect with absent ampullary segment and blocked fimbria were recorded. Ampullary fimbrial anastomosis was performed. Blocked ampullary end was excised. 'Fish-mouth' opening was created on the 'opened' ampullary end of the tube. The tips of the 'fish-mouth' opening of the tubes were anchored with two separate vicryl stitches. Through stab incision at the center of blind fimbria, the ends of anchoring stitches were pulled through the newly created fimbrial opening and fixed by everting lips of the fish-mouth on the outer surface of fimbria.

Out of three, one patient achieved a spontaneous pregnancy.

The steps of surgical correction of patients in Group-b have been demonstrated in the following diagrams (Fig-16)–

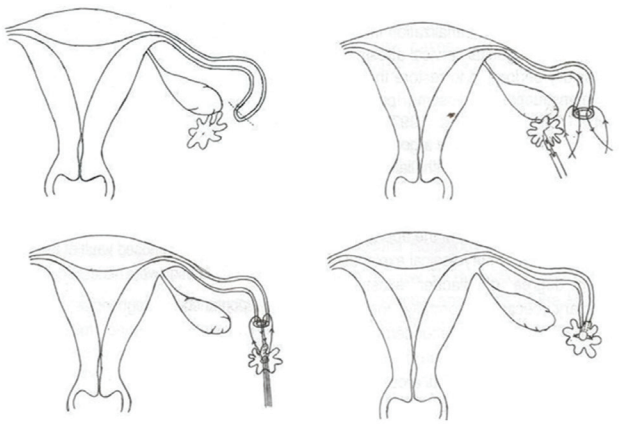


Fig-16: Pull through Technique — Ampullary Fimbrial Anastomosis

Embryologic explanation of the first two cases (Group a1 & a2): Around 6th week of gestation, infra-umbilical mesoderm intercedes between the bladder and cloacal membrane, - giving rise to origin of genital tubercle, lower abdominal wall and pubic rami. Failure of mesodermal invasion may lead to breakdown of cloacal membrane. This accident may result in exstrophy of bladder, deficient lower abdominal wall and pubic rami (Group-a1). In Group-a2, there was minimal degree of urethral exstrophy with total deficiency of abdominal muscles but skin was intact.

Special feature Group-b:

Currently IVF is the conventional treatment in these types of cases. But no case has been reported so far to achieve pregnancy by surgical procedure as reported in these patients.

Take Home Message

- Patients with mullerian anomalies usually present with three major clinical problems;- abnormal or absent menstrual cyclicity, problem in sexual function and impaired reproductive potential
- Surprisingly some of them remain asymptomatic (as in Gr-B3) and undiagnosed and are detected only during routine investigation of infertility and recurrent miscarriage
- Numerous classifications of mullerian anomalies have been suggested; some are too simple while others are very complex.
- Based on clinical presentation and anatomic defects, we have suggested a new classification
- Broad classification grouping consists of :- a) mullerian anomalies with a non functioning uterus b) mullerian anomaly with function uterus
- The anomalies with a functioning uterus have been further classified in relation to their anatomic varieties and degree of severity of clinical symptoms into three further sub-groups i) mullerian anomaly with a functioning uterus with complete outflow obstruction ii) mullerian anomaly with a functioning uterus with partial outflow obstruction iii) mullerian anomaly with a functioning uterus but without outflow obstruction
- Some of these anomalies are easily treatable or may not require treatment at all while in others, treatment may be extremely challenging.
- Lastly in addition to these commonly encountered groups of anomalies in clinical practice,- a few rare forms of mullerian defects have been observed with their treatment protocol have been illustrated in this presentation.

REFERENCE:

1. Rackow BW, Arici A. Reproductive performance of women with müllerian anomalies. Curr Opin Obstet Gynecol 2007;19(3):229–37
2. Acien P, Acien M. The presentation and management of complex female genital malformations. Hum Reprod Update 2016;22(1):48–69.
3. Counseller VS. Congenital absence of the vagina. JAMA 1948; 136:861.
4. Dietrich JE, Millar DM, Quint EH. Non-Obstructive Müllerian Anomalies. J Pediatr Adolesc Gynecol [Internet] 2014;27(6):386–95.
5. Tran ND, Hunter SK, Yankowitz J. Cme reviewarticle. Ginecol Obstet Mex 2004;59(6):456–63.
6. Parikh R, Nakum K, Kadikar G, Gokhle A. Mullerian anomalies: a cause of primary amenorrhea. Int J Reprod Contraception, Obstet Gynecol [Internet] 2013;2(3):393–7. Available from: http://www.ijrcog.org/index.php/ijrcog/article/view/115
7. Tanmahasamut P, Rattanachaiyanont M, Dangrat C, Indhavivadhana S, Angsuwattana S, Techatraisak K. Causes

of primary amenorrhea: A report of 295 cases in Thailand. J Obstet Gynaecol Res 2012;38(1):297–301.
8. Mats Brännström, Liza Johannesson, Hans Bokström, Niclas Kvarnström, Johan Mölne, Pernilla Dahm-Kähler, Anders Enskog, Milan Milenkovic, Jana Ekberg, Cesar Diaz-Garcia, Markus Gäbel, Ash Hanafy, Henrik Hagberg, Michael Olausson, Lars Nilsson, Livebirth after uterus transplantation,The Lancet, Volume 385, Issue 9968,2015,Pages 607-616
9. American Congress of Obstericians and Gynecologists, Mullerian agenesis: diagnosis, management and treatment. Committee Opinion No. 562. Obstet Gynecol 2013; 121: 1134.
10. Frank RT. The formation of an artificial vagina without operation. Am J Obstet Gynecol 1938;35:1053.
11. Ingram JM. The bicycle seat stool in the treatment of vaginal agenesis and stenosis: a preliminary report. Am J Obstet Gynecol 1981;140:867.
12. Abbe R. New method of creating a vagina in a case of congenital absence . Med Rec 1898;54:836.
13. McIndoe AH, Banister JB. An operation for the cure of congenital absence of the vagina. J Obstet Gynaecol Br Emp 1938;45:490
14. Wharton I.R. A simple method of constructing a vagina. Ann Surg 1938;107:842.
15. Chakravarty B N. Congenital absence of the vagina and uterus – simultaneous vaginoplasty and hysteroplasty, J Obstet Gynecol India 1977;27:627.
16. Chakravarty BN, Gun KM, Sarkar K. Congenital absence of vagina: anatomico-physiological consideration. J Obstet Gynecol India 1977;27:621.
17. Rothman D. The use of peritoneum in the construction of a vagina, Obstet Gynecol, 1972, vol.40 (pg. 835-838)
18. Baldwin JF. The formation of an artificial vagina by intestinal transplantation.Ann Surg1904;40:398
19. Goligher JC: The use of pedicled transplants of sigmoid or other parts of the intestinal tract for vaginal construction. Ann R Coll Surg Engl. 1983; 65: 353-5
20. ShirodkarVN.Contributionstoobstetricsandgynaecology. EdinburghE.&S.Livingstone,1960:84-108.
21. Vecchietti G. Neovagina nella syndrome di in RokitanskiKuster-Hauser. Attualita Obstet Ginecol. 1965;11:131–147
22. Davydov SN. 12 Jahre erfahrung mit der Kolpopoesis unter Verwendung von Peritoneum. Gynakologe. 1980;13:120–121
23. Kriplani A, Kachhawa G, Awasthi D, et al. Laparoscopic-assisted uterovaginal anastomosis in congenital atresia of uterine cervix: follow-up study. J Minim Invasive Gynecol 2012;19:477.
24. B. Chakravarty , R. Sankar Roy , S. C. Halder & A. Ganesh; Newer surgical approach to prevent re-stenosis following canalisation of cervico-vaginal atresia, Journal of Obstetrics and Gynaecology, 2015; Early Online: 1–2
25. P. Acie´n, M.I. Acie´n, F. Quereda and T. Santoyo; Cervicovaginal agenesis: spontaneous gestation at term after previous reimplantation of the uterine corpus in a neovagina: Case Report; Human Reproduction Vol.23, No.3 pp. 548–553, 2008
26. Baidyanath Chakravarty, Hiralal Konar, and Nagendra N. Roy Chowdhury; Pregnancies after reconstructive surgery for congenital cervicovaginal atresia. Am J Obstet Gynecol 2000;183:421-3
27. Ashalatha Ganesh, Nalini J. Gupta and Baidyanath Chakravarty; Surgical correction of rare M€ullerian anomalies and spontaneous pregnancies: a case report; Fertility and Sterility_ Vol. 89, No. 3, March 2008

Do Adenomyosis have Negative Impact on Reproductive Outcome in IVF Cycles?

Dr Ananya Basu, Dr Sourav Roy Choudhury and Dr Sunita Sharma

Introduction:

Adenomyosis is undoubtedly one of those intriguing conditions that infertility practitioners around the world find the most challenging to deal with. Previously it was thought to be a disease causing pain and bleeding abnormalities among the elderly women. But now it is considered as one of the prime factors affecting fertility, even in younger women. It was first described as ''fibrous tumors containing gland e structures that resemble endometrial glands,'' in 1860 by Karl Freiherr von Rokitansky. In 1972, Bird et al defined uterine adenomyosis as the benign invasion of endometrium into the uterine myometrium resulting in a diffusely enlarged uterus with microscopic, ectopic endometrial glands with stroma surrounded by hypertrophic and hyperplastic myometrium. International Classification of Diseases codes describe adenomyosis as "endometriosis of uterus and it is strongly associated with ovarian and pelvic endometriosis".. It can be found in 34.6% to 79% of women suffering from endometriosis compared with 19.4% in the control group. More advanced the endometriosis, higher is the incidence of adenomyosis with deeper uterine wall invasion compared with patients in other stages of endometriosis (42.8% vs 29.4%).

Pathogenesis:

A number of theories have been put forward to describe the origin of adenomyosis. The most widespread hypothesis is that adenomyosis originates from the invagination of the endometrial basalis into the myometrium. The metaplastic theory suggests that adenomyotic lesions develop from metaplasia of displaced embryonic pluripotent remnants or from differentiation of endometrial and stromal stem cells deposited in the myometrium after retrograde menstruation. Another theory describes adenomyotic

Sonographic criteria for diagnosis of different variants of adenomyosis

2D US features	Diffuse adenomyosis	Focal adenomyosis	Adenomyoma
Serosal contour of the uterus	Often globally enlarged uterus	Often regular	Lobulated or regular
Definition of lesion	III-defined	III-defined or well defined in cae of cystic or hyperecohoic lesions surrunded mostly by normal myometrium	May be well defined surrounded by hypertrophic myometrium
Symmetry of uterine walls	Myometrial a nterior-posterior or lateral asymmetry	Often symmetric	Asymmetrical in presence of well-defined lesion
Shape	III-defined	III-defined, oval in case of cystic lesions	Round, oval, lobulated
Contour	III-defined	Irregular or ill-defined	Regular or ill-defined
Shadowing	No edge shadows Fan shaped shadowing Linear hypoechoic striation	No edge shadows Rarely fan shaped shadowing, or linear hypoechoic striation	Edge shadows may be present Internal, often fan-shaped shadowing
Echogenicity	Nonuniform diffuse Presence of intramyometrial diffuse areas of: • mixed echogenicity • small cyst • hyper-echogenic islands • subendometrial echogenic lines	Focal, often isolated surrounded by normal myometrium Presence of intramyometrial focal small areas of: • mixed echogenicity • small and large cyst • hyperechogenic islands • subendometrial echogenic lines or buds	Focal, loubulated Presence in hyper-, iso-, hypoechogenic intramyometrial lobulated areas of: • mixed echogenicity • small and large cyst • hyperechogenic islands
Vascularity	Translesional flow Diffuse minimal or few vessels	Diffuse minimal Sporadic vessels	Translesional flow Diffuse vessels or circumferential flow
Endometrial rim	Irregular or ill-defined Distorted or imprinted	Often regular or imprinted by subendometrial focal lesion	Often regular or distorted by the lobulated lesion

Source- Lazzeri. Sonographic mapping of adenomyosis. Fertil Steril 2018

lesion as basalis invagination proceeding along the intramyometrial lymphatic system.

Diagnosis of adenomyosis:

It is challenging to diagnose adenomyosis, as no clear consensus has been reached on the investigation of choice. New imaging tools like Ultrasound and magnetic resonance imaging (MRI) enable us to detect adenomyosis as a clinical entity, which was earlier thought to be a histological diagnosis solely. The systematic use of these techniques allows visualization of the myometrial architecture's distortions in a noninvasive way, also distinguishing between the pathology of the outer and the inner myometrium or junctional zone (JZ).

2-D and 3-D TVS and MRI can diagnose adenomyosis with similar accuracy. Some clinicians, however, have recommended the use of MRI over two-dimensional TVS in detecting adenomyosis owing to its improved specificity and sensitivity. Considering the widespread availability of ultrasonography and relatively low cost, it is the most feasible diagnostic method available for adenomyosis. A new scoring system was introduced by Lucia et al for uterine adenomyosis is reproducible and could be useful in clinical practice. Proper training of sonographer with standardization of TVS approach are needed for a correct diagnosis of myometrial disease.

Adenomyosis: is it a cause of infertility and poor pregnancy outcome?

The causal association of adenomyosis with infertility has not been fully established, and its effects on natural conception and success of fertility treatment are also not very clear. The proposed mechanisms responsible for infertility and poor reproductive outcome in adenomyosis may be abnormal junctional zone myometrium leading to dysregulation of uterotubal contractility, altered endometrial function and receptivity and abnormal decidualization. Dysperistalsis of cycle dependent contractions of the junctional zone in the patients with adenomyosis results in a more pronounced retrograde menstruation and a disturbed utetine tubal sperm transport. Inflammatory reactions mediated by prostaglandins and cytokines may also alter uterine contractions, leading to impaired utero-tubal sperm transport. Another probable cause is excessive free radical formation leading to deterioration of oocyte quality and embryo development and activation of macrophages, T-cells and increased nitric oxide exposure, resulting in abnormal implantation and early miscarriage. As the junctional zone plays an important role in deep placentation, it is likely that pre-conception abnormality of the junctional zone predisposes a woman to adverse pregnancy outcome like preterm delivery, PPROM and SGA.

Proposed causes of infertility in patients with adenomyosis

1. Abnormal utero-tubal transport:

A) Uterine abnormalities
B) Abnormal architecture and function of the myometrium
C) Uterine dysperistalsis

2. Altered endometrial function and receptivity

A) Abnormal metabolism in endometrium
   i) Altered steroid metabolism in the endometrium
   ii) Increase in inflammation in uterus
   iii) Abnormal estrogen and progesterone receptor expression
B) Excessive generation of free radicals and oxidative stress in uterus
C) Impairment of implantation
   i) Reduced expression of adhesion molecules
   ii) Lack of expression of implantation markers
   iii) Genetic alterations affecting embryonic development

Abnormal utero-tubal transport	Altered endometrial function and receptivity
• Uterine abnormalities • Abnormal architecture and function of the myometrium • Uterine dysperistalsis	*Abnormal metabolism in endometrium* • Altered steroid metabolism in the endometrium • Increase in inflammation in uterus • Abnormal estrogen and progesterone receptor expression *Impairment of implantation* • Reduced expression of adhesion molecules • Lack of expression of implantation markers • Genetic alterations affecting embryonic development *Excessive generation of free radicals and oxidative stress in uterus*

Proposed treatment modalities for adenomyosis:

No systematic study of any medical regimen aimed at treating infertility associated with adenomyosis has ever been attempted. Adenomyosis in infertile women can be treated surgically or medically with the use of GnRH agonist (GnRHa). It is generally thought that GnRH agonists can suppress ovulation and the production of estrogen and thus lead to the atrophy of the ectopic endometrium. It is also said that GnRH agonist therapy significantly reduces the inflammatory reaction and angiogenic response and induces considerable apoptosis in different tissues of patients with adenomyosis. Several case reports or small series have been published of successful treatment of adenomyosis-associated infertility with GnRHa, given alone or in combination with surgery. None of the proposed treatments like estrogen-progesterone combinations, danazol, LNG-IUS, uterine artery embolisation or MRI-assisted high-intensity focused ultrasound (HIFU) ablation, can improve fertility outcomes in patients with adenomyosis. IVF remains the mainstay of management of most of adenomyosis related infertility. Limited studies have investigated assisted reproductive technology (ART) outcome in women with adenomyosis. Some earlier studies have reported negative reproductive outcomes with adenomyosis; however, others have failed to observe such an association.

We also conducted a retrospective study, where we aimed at investigating IVF and intracytoplasmic sperm injection (ICSI) outcomes after gonadotrophin releasing hormone (GnRH) agonist downregulation in patients with ultrasonically diagnosed uterine adenomyosis. The details of the study are described below.

Materials and methods:

This retrospective cohort study was carried out at the Institute of Reproductive Medicine, Saltlake, Kolkata, India, between January 2010 and January 2015. A total of 1165 women with endometriosis, adenomyosis, or both, and tubal factor infertility undergoing their first cycle of IVF–ICSI treatment were studied. The inclusion criteria for the study were:- women undergoing their first cycle of IVF; Grade III and IV endometriosis confirmed by laparoscopy; adenomyosis diagnosed on two-dimensional TVS; and tubal factor infertility diagnosed on hysterosalpingography or laparoscopy. Women with adenomyosis who underwent myolysis or wedge resection surgery; women with an endometrioma larger than 4 cm; women with fibroid, hydrosalpinx or uterine size greater than 12 weeks and poor ovarian reserve, were excluded from the study. Once the inclusion and exclusion criteria had been applied, 973 out of the 1165 women were selected and divided into four groups: tubal factor infertility (controls: n = 466); endometriosis alone (Group A: n = 355); endometriosis with adenomyosis (Group B: n = 88); and only adenomyosis (Group C: n = 64) (Figure 1). Patients were diagnosed with adenomyosis after visualizing at least three sonographic criteria on two-dimensional TVS, such as globular uterus caused by overall increase in myometrial thickness (n = 152); asymmetrically thickened anterior or posterior myometrial wall (n = 130); poorly defined endo-myometrial interface (n = 90); presence of heterogeneous myometrial area (n = 152); and myometrial cysts (n = 35). All patients had received a depot preparation of the GnRH agonist leuprolide acetate 3·75 mg (Lupride 4; Sun Pharmaceuticals, Mumbai, India) in three doses every 28 days. After confirmation of ovarian suppression 3 weeks after the last dose, recombinant FSH (150–300 IU; Gonal-F; Serono, Aubonne, Switzerland) was started. Ovarian folliculometry was carried out from day 6 of stimulation and then gonadotrophin doses were titrated accordingly. When a minimum of two follicles reached a diameter of 17 mm or wider, HCG injection was administered (10,000 IU; Profasi; Serono, Geneva, Switzerland). Serum peak oestradiol was assessed on the day of HCG administration. Oocytes were retrieved transvaginally under ultrasound guidance 34–36 h after HCG injection. Conventional IVF–ICSI was subsequently carried out. Day 2 or day 3 grade I embryos were transferred according to availability and development stage of embryos. Luteal support began on the day of embryo transfer with intravaginal progesterone gel (90 mg) daily. Serum beta-HCG level was measured 14 days after embryo transfer and, if positive, luteal support was continued up to 12 weeks of pregnancy.

Results:

Baseline and cycle characteristics were found to be identical in all the four groups .Number of

oocytes retrieved and fertilization rates were also comparable in all the three groups (Table 1). The clinical pregnancy rate was 36.62% in women with endometriosis alone, 22.72% in women with endometriosis and adenomyosis, 23.44% in women who only had adenomyosis and 34.55% in controls (Table 2). Miscarriage rates were: 14.62%, 35%, 40% and 13.04%, respectively. Live birth rates were 27.47% in the controls; 26.48% in women who had only endometriosis; 11.36% in women with both endometriosis and adenomyosis; and 12.5% in women who had only adenomyosis (Table 2). Live birth was observed to be reduced in adenomyosis groups compared with controls and women with only endometriosis. No statistically significant difference was observed in clinical pregnancy, miscarriage or live birth rate between controls and women with only endometriosis. Live birth rate was found to be significantly different between controls and women with adenomyosis only (P = 0.01) and women with endometriosis and adenomyosis (P = 0.002).

Pregnancy-associated complications, like antepartum haemorrhage, preeclampsia, IUGR, severe preterm delivery, IUD and postpartum haemorrhage are shown in Table 3. Non-viable severe preterm births and IUD for controls, Group B and C were 12, 3 and 1, respectively; and for Group A, two severe preterm babies survived out of 19 such cases. It was found that different pregnancy-related complications were slightly higher in patients with adenomyosis (Group B and C) compared with controls and Group A. The numbers were too small in both groups to imply any statistical significance (Table 3), except for IUGR, when controls were compared with Group B and C together (Table 3). The patients with adenomyosis (Groups B and C) were again classified into three sub-groups depending on the number of sonographic criteria fulfilled for diagnosis. These sub-groups were: patients diagnosed only with three sonographic criteria; only four sonograhic criteria; and all five criteria. The representation of the patients in each of these sub-groups and their pregnancy outcomes are depicted in Table 4. Adenomyosis patients selected through higher number of sonographic criteria (five-criteria) have marginally high miscarriage rates and lower live birth rates compared with patients selected through three or four criteria. The numbers, however, were too small for any statistical significance. The characteristics of the endometriosis groups included are presented in Table 5.

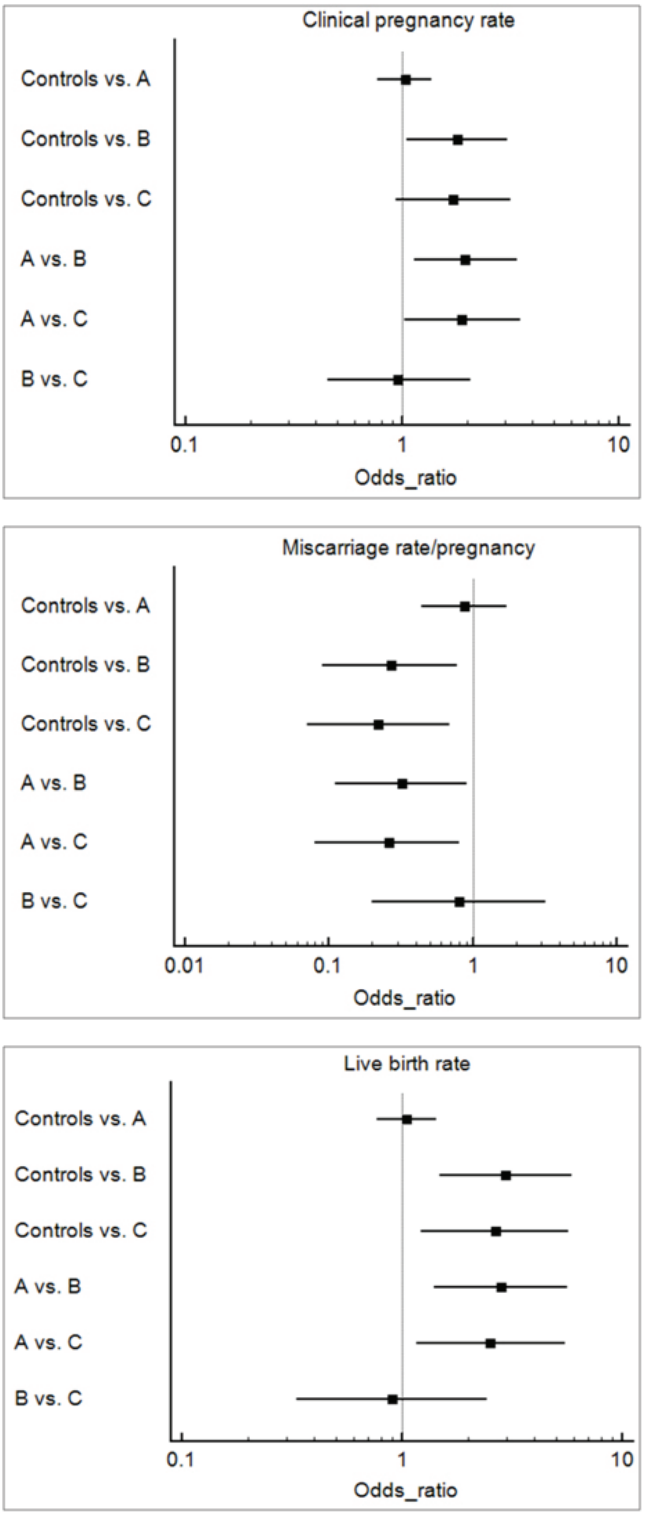


Figure1: Forest plots comprising different group analysis and depicting significance of (a) clinical pregnancy rate; (b) miscarriage rate per pregnancy; and (c) live birth rate between the four groups: controls (tubal); group A (endometriosis); group B (endometriosis + adenomyosis); and group C (only adenomyosis).

Table 1: Baseline and cycle characteristics

Parameters	Tubal (controls) (n = 466)	Endometriosis (group A) (n = 355)	Endometriosis + adenomyosis (group B) (n = 88)	Adenomyosis (group C) (n = 64)
Age (years)	33.02 ± 3.4	32.67 ± 2.53	32.12 ± 3.03	32.89 ± 2.98
Duration of infertility (years)	7.3 ± 3.2	7.6 ± 2.35	7.9 ± 3.09	8.01 ± 2.1
BMI (kg/m2)	24.25 ± 3.02	23.72 ± 3.03	24.39 ± 3.69	24.09 ± 3.42
AFC	9.16 ± 4.28	8.6 ± 2.37	8.48 ± 1.90	9.01 ± 2.2
AMH (ng/ml)	2.89 ± 0.87	2.77 ± 0.64	2.75 ± 0.72	2.85 ± 0.79
Dose of gonadotrophins (IU)	2196.48 ± 1163.88	2390.78 ± 1148.29	2359 ± 1100.48	2232.77 ± 678.43
Oestradiol on day of HCG (pg/ml)	1270.71 ± 624.36	1370.22 ± 521.87	1287.73 ± 577	1366.16 ± 598.26
Number of MII oocytes retrieved	8.8 ± 2.6	8.44 ± 1.72	8.36 ± 1.6	8.6 ± 2.2
Fertilization rate (%)	73.52 ± 5.94	73.14 ± 5.71	72.52 ± 6.7	73.87 ± 6.29
Number of grade I/II embryos	3.6 ± 1.66	3.38 ± 1.38	3.20 ± 1.09	3.55 ± 1.31

AFC, antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index; MII, metaphase II. Data are expressed as mean ± SD. No statistically significant differences were observed between the two groups.

Table 2: Pregnancy outcome parameters

Pregnancy outcome	Tubal (controls)	Endometriosis (group A)	Endometriosis + adenomyosis (group B)	Adenomyosis (group C)
Clinical pregnancy rate, n (%)	161/466 (34.55)	130/355 (36.62)	20/88 (22.72)	15/64 (23.44)
Miscarriage rate/pregnancy, n (%)	21/161 (13.04)	19/130 (14.62)	7/20 (35)	6/15 (40)
Live birth rate, n (%)	128/466 (27.47)	94/355 (26.48)	10/88 (11.36)	8/64 (12.5)

Non-viable severe preterm and intrauterine demise for controls; group B and C were 12, 3 and 1, respectively; for group A, out of 19 such cases, two severe preterm babies survived.

Table 3: Comparison of pregnancy complications

	Tubal (controls)	Endometriosis (group A)	Endometriosis+ adenomyosis, and only adenomyosis (groups B + C)	Controls versus group B + C	Group A versus group B+C
PPH	13/140	11/111	2/22	OR 1.02 (95% CI 0.21 to 4.78) P = NS	OR 1.10 (95% CI 0.22 to 5.34 P = NS
APH	9/140	8/111	1/22	OR 1.10 (95% CI 0.22 to 5.34) P = NS	OR 1.63 (95% CI 0.19 to 13.74) P = NS
PET	7/140	9/111	4/22	OR 1.55 (95% CI 0.44 to 5.43) P = NS	OR 2.60 (95% CI 0.77 to 8.7) P = NS
IUGR	7/140	13/111	5/22	OR 0.17 (95% CI 0.05 to 0.62) P = 0.007	OR 0.45 (95% CI 0.14 to 1.42) P = NS
Severe preterm	9/140	14/111	3/22	OR 0.43 (95% CI 0.10 to 1.75) P = NS	OR 0.91 (95% CI 0.23 to 3.49) P = NS
IUD	3/140	5/111	1/22	OR 0.48 (95% CI 0.05 to 4.84) P = NS	OR 1.03 (95% CI 0.11 to 9.32) P = NS

APH, antepartum haemorrhage; IUD, intrauterine demise; IUGR, intrauterine growth restriction; PET, pre-eclampsia; PPH, postpartum haemorrhage. All data are as per ongoing pregnancy, defined as viable intrauterine pregnancy of at least 12 weeks'gestation confirmed by ultrasound. NS, non-significant P-values.

Table 4: Sonographic criteria for adenomyosis and pregnancy outcome

Sonographic criteria	Endometriosis + adenomyosis (group B)			Adenomyosis (group C)		
	Only three criteria	Only four criteria	All five criteria	Only three criteria	Only four criteria	All five criteria
Total adenomyosis patients, n (%)	22/88 (25)	36/88 (40.9)	30/88 (34.1)	11/64 (17.2)	24/64 (37.5)	29/64 (45.3)
Clinical pregnancy rate, n (%)	8/88 (9.1)	6/88 (6.8)	6/88 (6.8)	5/64 (7.8)	6/64 (9.4)	4/64 (6.3)
Miscarriage rate/-pregnancy, n (%)	1/20 (5)	3/20 (15)	3/20 (15)	0/15	2/15 (13.3)	4/15 (26.7)
Live birth rate, n (%)	4/88 (4.5)	3/88 (3.4)	3/88 (3.4)	4/64 (6.32)	2/64 (3.)	2/64 (3.1)

Table 5: Characteristics of endometriosis in different groups

Characteristics of endometriosis	Endometriosis (group A; n = 355)	Endometriosis + adenomyosis (group B; n = 88)
Unilateral endometrioma, n (%)	139 (39.15)	31 (35.23)
Bilateral endometrioma, n (%)	74 (20.85)	33 (37.5)
Endometriotic nodules, n (%)	67 (18.87)	9 (10.23)
Endometrioma + nodules, n (%)	75 (21.13)	15 (17.054)
Size of endometrioma,an (%)		
<2 cm	72 (25)	17 (21.25)
2–3 cm	130 (45.14)	42 (52.5)
3–4 cm	86 (29.86)	21 (26.23)

A total of 288 patients in group A and 80 in group B had endometrioma.

Discussion:

This study reveals that adenomyosis has an adverse impact on IVF–ICSI outcome either alone or in the presence of endometriosis compared with women who only have endometriosis or tubal factor infertility (controls). It is well known that prevalence of adenomyosis is higher among subfertile women, especially in association with pelvic endometriosis. In our Institute, incidence of adenomyosis alone is 13.78% in patients undergoing IVF, while presence of coexisting adenomyosis in women with endometriosis is much higher, i.e.,42.11%. Interestingly, we found that mean age of the study groups was less (32.12 ± 3.03 to 33.02 ± 3.4), considering the average duration of infertility ranging from 7–8 years. Relatively longer durations of infertility in this study may be attributed to the early age of marriage and childbearing which is very common in India. Moreover, couples usually are late in reporting to a tertiary care infertility clinic because of lack of proper knowledge and awareness and economical constraint is also another important factor for delaying the initiation of the treatment.

As already mentioned, we had used 2D TVS as our diagnostic tool. Patients diagnosed with 4 Ultrasonic criteria were found to have worse outcomes, although this was not statistically significant and therefore it can be inferred that patients associated with higher grades of adenomyosis are more likely to have a detrimental effect on reproductive outcome. This may be one of the reasons for observing comparatively poor obstetric outcome of adenomyosis patients who were recruited for our study. Our study reported a significant increase in miscarriage rates in patients with adenomyosis compared with patients with only endometriosis or controls, in spite of having identical numbers of good-quality oocytes and embryos. This implies that chances of miscarriage are higher in the patients with adenomyosis, regardless of the quality of oocyte or embryo. In the current study, other than obstetrical complications like pre-eclampsia and severe preterm delivery, IUGR was observed to be significantly higher in the adenomyosis group (Group B and C) compared with controls. The numbers were also higher in Group B and C compared with the only endometriosis (Group A). But this observation was not statistically significant, possibly because of the small number of such cases in each group (Table 3).

Prolonged down-regulation with GnRH agonists may improve reproductive outcome in adenomyosis patients as proposed by some investigators. We also agree that pre-treatment with GnRH agonists leads to an overall improvement in the endometrial milieu and hence, should be a logical intervention to optimize obstetric outcomes in adenomyosis. But prolonged pituitary suppression will undoubtedly affect ovarian response to stimulation and therefore, decrease the number as well as quality of the oocytes retrieved. Therefore, we administered only three doses of GnRH agonists before commencing IVF stimulation. Unlike the study conducted by Landi et al. (2008), our study did not find similar pregnancy rates in adenomyosis groups compared with controls. This is possibly due to GnRH agonist, which may have had a positive effect on endometrial environment but not to an extent that it completely abolishes the harmful effects of the disease.

Conclusions:

To conclude, it can be said that the presence of adenomyosis seemingly has adverse effects on IVF outcomes in terms of clinical pregnancy rate, live

birth rate and miscarriage rate. Thus screening for adenomyosis needs to be considered before ART so that the couple can understand the prognosis better. Hence, counseling of women with adenomyosis before starting IVF treatment is of paramount importance. Possibilities of decreased success after IVF treatment and complications of pregnancy should be explained beforehand to the couple where the woman has been identified with adenomyosis. Down-regulation with GnRH agonists in more severe grades of adenomyosis may not always improve IVF outcome.

Further reading:

1) Pathogenesis of uterine adenomyosis: invagination or metaplasia? García-Solares, Javier et al. Fertility and Sterility, Volume 109, Issue 3, 371 – 379

2) A sonographic classification of adenomyosis: interobserver reproducibility in the evaluation of type and degree of the myometrial involvement; Lazzeri, Lucia et al. Fertility and Sterility, Volume 110, Issue 6, 1154 - 1161.e3

3) Does presence of adenomyosis affect reproductive outcome in IVF cycles? A retrospective analysis of 973 patients; Sunita Sharma, Shikha Bathwal, Nupur Agarwal, Ratna Chattopadhyay, Indranil Saha, Baidyanath Chakravarty, Reproductive BioMedicine Online, Volume 38, Issue 1, 13 – 21

4) Tesone, M., Bilotas, M., Baranao, R.I., Meresman, G. The role of GnRH analogues in endometriosis-associated apoptosis and angiogenesis. Gynecol Obstet Invest 2008; 66: 10

5) Vercellini, P., Consonni, D., Dridi, D., Bracco, B., Frattaruolo, M.P., Somigliana, E. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and metaanalysis. Hum Reprod 2014; 29: 964–977.

Work Statement of Patients for the month of July to September 2019

Total No of Gynaecological & Obstetric Cases attended		**829**
No of Gynaegological Cases	628	
No of Obstetric Cases	201	
Gynaegological Cases		
Infertility		**573**
Primary	413	
Secondary	160	
Other Gynaecological Cases		**20**
History of Recurrent Spont Miscarriage(> 3)		**18**
History of Unexplained Spont Miscarriage (<3)		**14**
History of Recurrent Pregnancy Loss		**3**
Categorization of Infertility/Gynaecologocial Cases		
Female Factor	232(40.49%)	
Male Factor	230 (40.13%)	
Unexplained	84(14.46%)	
Combined Factor	27(4.71%)	
Total No of IVF & IUI Cycles		**572**
IVF		
Fresh Cycle	139	
ET Done	80	
ET not done	59	
Cryo Cycle	113	
IUI		**320**
Obstetric Cases		
Total Pregnancy folowing		**201**
Medical treatment (Induction Ovulation)	49	
Surgical Treatment	12	
During investigation	46	
Intrauterine Insemination	35	
IVF-ET including FET Cycle	59	
Pregnancy Loss		**21**
Missed Abortion	8	
Anembryonic Sac	4	
Biochemical	7	
Ectopic	2	
Elective Termination		
Spont. Termination		
RSM (> 3)	0	
USM (<3)	0	
RPL	0	
Clinical Pregnancy		**180**
Viable Deilvery		**38**
Nature of delivery		
CS		38
Normal		0
Sucessful Delivery after		
IVF		13
IUI		3
OI		10
Spont.		2
During investigtion		10
Baby outcome		
Alive		**45**
Singleton	31	
Male	20	
Female	11	
Twins	14(7 pair)	
Male	6	
Female	8	
Neonatal Death	0	
Still Born	2	
Gynaecological Surgery		**38**
Laparoscopy + Hysteroscopy	18	
Hysteroscopy	9	
Laparoscopy	-	
Ectopic	4	
T- Insersion	-	
D&E	2	
MCDonald	4	
Fentons	1	