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Research Article

PREVENTION OF INTRA UTERINE ADHESION FOLLOWING HYSTEROSCOPY PROCEDURE: A REVIEW OF LITERATURE

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A B S T R A C T

Back ground: Intra uterine adhesions have been recognised as a cause of secondary amenorrhoea since the end of 19th century [1]. IU adhesions are a rare but significant cause of menstrual disturbances and secondary infertility [2.] They are likely to form after any endo- uterine surgery via deregulated activation of coagulation chain linked to the inflammatory process [3.]

Objective: The purpose of this review was to perform a systematic study and analysis to evaluate the effectiveness of post operative prevention strategies on intra uterine adhesion formation following operative hysteroscopy.

Materials and Method: Systematic computer based literature search was conducted to provide a survey of the various measures used in hysteroscopy surgery to prevent adhesions in accordance with PRISMA (preferred reporting items for systematic reviews and meta analysis) guidelines.

Searches were conducted in Medline, Pub Med, Cochrane Library, ErMed, Scopus and World of science databases using the keywords 'prevention', 'intrauterine Adhesions', 'asherman syndrome', 'post operative', 'uterine synechae', 'endo uterine surgery'. The search included studies from the earliest publication from 1985 date to publication 2016 in English literature.

Inclusion criteria were studies preferably randomised control studies or observational studies (prospective or retrospective cohort) comparing any preventive measures of intrauterine adhesions after hysteroscopy were included in review. The main outcome measure was a reduction in post operative intrauterine adhesion.

Results: Five studies evaluated intra uterine devices and three studies evaluated hyaluronic acid gel, 3 studies evaluated hormones and other medications and 5 studies evaluated effect of stem cells in re generation of uterine endometrial layers**.** The results of our study shows that (1) surgical techniques which uses less electro cautery should be preferred over others (2) non copper containing barrier are the most widely used methods and gel barrier have been proven to have significant clinical effect (3) early second look hysteroscopy would appear to be an effective preventive strategy before the adhesions settles down. (4) the role of hormones and antibiotics have been used in combination with other methods so efficacy if the individual substance is difficult to evaluate (5) Autologous stem cells are showing very promising results and will be effective tool in future.

Conclusions: There is lack of definite evidence to conclude that any particular treatment is effective in preventing post hysteroscopic uterine adhesion formation [4]. Robust and high quality randomised trials are still needed to assess the effectiveness of different anti adhesion therapies before any of these strategies may be strongly recommended for improving clinical outcomes in women treated by operative hysteroscopy[5].

INTRODUCTION

Back ground

Intra uterine adhesion or Asherman syndrome is described as partial or complete obliteration of the uterine cavity by adherence of uterine wall leading to infertility, menstrual abnormalities and habitual abortion[1].

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Heinrich Fritsch in 1984 first described post traumatic IUA in a patient who developed secondary amenorrhea following curettage for bleeding on 24th postpartum day[2]. Since the end of 19th century IUA is recognised as one of the cause for secondary amenorrhoea [3]. The literature shows that the rate of IUA reformation after endo uterine surgery is around 3.1 to 23.5 % [4,5,6.]. It is described that these adhesions usually are flimsy and thin[7].

After any endo- uterine surgery Intra uterine adhesions are likely to occur via deregulated activation of coagulation chain linked to the inflammatory process[8]. Veit in 1895 reported the first treatment of IUA. He negotiated a fine needle through the

uterine cervix, after which he performed a dilatation upto Hegar 10 [9] Kustner[10] later on in the same year divided IUA by means of hysterotomy via the pouch of Douglas[10]. Wolf in 1926 carried out lysis of adhesion by laparotomy [11] and Asherman [12] did in 1950. Netter[13] advocated the insertion of a finger or curette throughout the cervix or at hysterotomy for separation of IUA. But all workers concluded that results were not very satisfactory after 10 years of applying this mode of treatment and advised avoiding surgical intervention for the treatment of IUA.

Two factors were responsible for this partial failure of surgical treatment: one is Formation of new adhesions and the other is severe endometrial damage or sclerosis. In order to overcome this Strassman implanted and later on he tried transplantation of endometrium inside the uterine cavity [14]. Carmichael tried to transplant fetal membranes following adhesiolysis. He also suggested packing the uterus with gauge strip or tampons with estrogens and antibiotics[15]. Unfortunately the range of this procedures did not yield very satisfactory or encouraging outcome. Many authors [16, 17, 18, 19, 20, 21, 22, 23, 24, 25] have reported formation of further adhesions on dividing adhesions by hysterotomy rather than via vaginal route. The results of the hysterotomy method in 31 cases compiled from 12 reports show that only 16 patients(52 %) conceived and although 8(26%) gave birth to a healthy child 4 (13%) patients had to be exposed to ceserean hysterectomy subsequently to placenta accereta.

We are trying to find an answer for what should be the ideal post operative adhesion preventing agent following an hysteroscopic adhesiolysis procedure following a literature survey from the available data base.

Etiology of adhesion formation[26]

The following tables lists the possible etiological factors regarding intra uterine adhesions.

Table 1 Predisposing and causative factors of intra uterine adhesion formation [26]Reproduced from: C.Nappi1, A.Di Spiezio Sardo, E.Greco1, M.Guida, S.Bettocchi and G.Bifulco Prevention of adhesions in gynaecological endoscopy: Human Reproduction Update, Vol.13, No.4 pp. 379–394, 2007 doi:10.1093/humupd/dml061

Pathophysiology

A prospective study which involved 40 patients with IUA, Doppler velocimetry observed an high impedance of spiral artery of uterine myometrium by Malhotra *et al*. The authors hypothesized that these phenomenacould explain the reduced endometrial receptivity and endometrial regeneration in these group of women [27].

Patients who are showing response to treatment, it was observed that vascular endothelial growthfactor (VEGF) and microvessel density are significantly increased, so angiogenesis and revascularization may play a significant role in regeneration of endometrium. [28].

Adhesion related cytokines are also actively involved in the pathogenesis of IUA (eg. b-fibroblast g Growthfactor, Platelet derived growth factor and transforming growth factor type 1) [29]

A genetic factor could explain why certain patients show more frequent adhesions incidence and recurrence, or why IUA adhesions can develop even without any surgical traumaor trigger event although the factor is not clearly identified till date [30,31,32]

MATERIALS AND METHOD

A systematic review was conducted in accordance with PRISMA (preferred reporting items for systematic reviews and meta-analysis) guidance.

Search Strategy*:* All eligible studies were identified on computerised database (Pub med, ErMed, Scopus and Web of Science using the keyword 'prevention', 'hysteroscopy', 'intrauterine adhesion', 'uterine synechae', 'post endouterine surgery'.The search included studies from the earliest publications dated 1985 to 2016. Additional relevant articles were identified from citations within these publications.

Study Characteristics*:* All observational, prospective or retrospective studies, case series, randomised control study were collected. We divided the collected data into 4 groups based on their prevention methodology which is described in the following table.

Predisposing factors	
Individual predisposition	A severe form of IUA is found in certain patients while others remains unaffected undergoing the same procedure. This leads to the development of an theory of individual constitutional factor: why some patients respond well to certain treatment where as others experience recurrent adhesions and also explain why some develop adhesions in the absence of any trauma. (Shenker andMargalioth, 1982).
Gravid uterus	Softening of the uterus happens once pregnancy takes place. Any trauma in the form of repeated curettage results in exposing the basal layer of the Endometrium with subsequent loss of the regenerative mechanism. Curettage between the second and fourth week after delivery brings forth more damaging changes to the basal layer. (March, 1995; Schenker, 1996).
Infections	There is no direct connection between clinical infections and IUA (Schenker, 1996) although pelvic TB related IUA was suspected .
Retained placenta remnants	increased fibroblastic activity takes place with collagen formation before endometrial regeneration has taken place (Polishuk et al., 1975).
Breast-feeding	Nursing mother remains in a relative estrogen deficient for a prolonged period and thus endometrial regeneration is lacking (Baggish Barbot and Valle, 1999).
Causative factors : Traumma Forced intrauterine intervention/Post-partum or post-abortion dilatation and curettage	Trauma of the endometrium (Baggish Barbot and Valle, 1999).
Operative hysteroscopy Uterine surgery (e.g. caesarean section, myomectomy)	Trauma of the endometrium (Baggish Barbot and Valle, 1999).
Pelvic irradiation Genital infections (tubercolous endometritis, puerperal	Chronic inflammation of the endometrium (Baggish Barbot and Valle, 1999).

Table 2 Agents which can be used to prevent further adhesion formation

Group 1 : Barrier : Physical Barrier	1. IUD 2.Intra uterine Balloon stent 3. Foleys cather/ words cather .
Gel barrier	1. Auto cross linked Hyaluronic acid (Hyalobarrier)) 2. Modified Hyaluronic acid (HA) and Carboxy Methylcellulose (CMC).(seprafilm) 3. Poly ethylene oxide and Carboxy Methyl Cellulose stabilised by Calcium Chloride . 3. Alginate carboxymethyl cellulose hyaluronic acid
Group 2 : 1. Hormones 2.Anti inflammatory agents 3.Drugs to improve the vascular flow to endometrium	1.Estrogen , 2. Steroids , NSAID , aspirin , ketorolac 3. Sildenafil
Group 3 : Regenerative medicine and Stem cells	Stem cell derived from endometrium (sheded during menstruation) Bone marrow stellcells
Group 4 : Miscellaneous	Second look adhesiolysis, amnion graft, oral mucosal sheet plate rich plasma

DISCUSSION OF EACH METHOD

Group: 1

Physical Barrier: Intra Uterine Devices

Use of IUD to prevent adhesion recurrence was one of the first attempt that was documented in the literature [33] **.** When placed between the uterine cavity it provides a dynamic physical barrier between the uterine walls separating the endometrial layers after lysis of IUAs [34, 35, 36 37]. An inert loop (eg Lippes loop) is considered IUD of choice when treating IUAs although it is no longer available in many geographic areas[38].

Polishuk and Weinstein described a particular device known as Soichet intrauterine device in the prevention of intra uterine adhesion after uterine curettage. They reported the incidence of readhesion formation to be very low and dropped significantly compared to other IUDs [39].

Copper containing and T shaped IUDs are generally not recommended because of their inflammatory provoking properties and small surface area[40,41]. Similarly levonorgesterol releasing IUD are also discouraged for its suppressing effects on endometrium. Contrary to this belief Vasce *et al* showed good results who used a copper IUD in forty eight (48)women with functional amenorrhoea after the insertion of IUD, a significant number of women regained a regular menstuation in short follow up [42] From another non randomised study it was observed that there was no significant difference in formation of adhesion amongst post operative IUD with or without hormone therapy [43] Although the benefit of inserting the IUD is significant there is risk of infection when an IUD is introduced into uterus immediately after adhesiolysis which is estimated to be 8 % and perforation of the uterus during IUD insertion has also been reported [44].

Fig 1 Soichets Intrauterine device

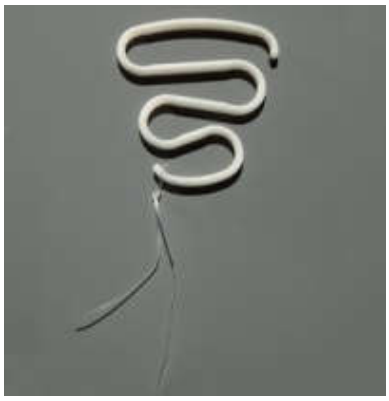

Fig 2 lippes loop Photo: Jamie Chung;

(Manufacturer and Distributor Syntex Laboratories) IUD Courtesy of Dittrick Medical History Center and Museum/Case Western Reserve University https://scholarsrepository.llu.edu/thomsen-contraceptive/28/ https://www.wired.com/2011/07/ff_iud/

Table 3 Summary of the previously published studies (2008 – 2013) that used various techniques of IUD therapy and ancillary treatment in patients with intra uterine adhesions [75]

Source and year	Type of IUD	Duration of IUD	Adjuvant therapy			
			Hormone	Foleys	Hyaluronic acid	Amnion graft
Pabuccu 2008 [45]	Lippes loop	2 months	Yes	No	No	No
Roy *et al* 2010 [46]	CuT	30 days	Yes	No	No	No
Salma 2011 [47]	Uterine shaped	1 month	Yes	No	Yes	No
Myers Hurst 2012 [48]	Copper	4- 10 weeks	Yes	No	No	No
Mohamed 2012 [49]	Copper T 380 A	1- 3 months	Yes	No	No	Yes
Yamamoto & Takeuchi 2013 [50]	Not reported	2 cycles	Yes	No	No	No
Lin *et al* 2013 [51]	Copper coil	2 months	Yes	No	Yes	No
Sendag *et al* 2013 [52]	Cu T	1-3 months	Yes	No	No	No

Reproduced from[75]: Salma U, Xue M, sayed A, Xu D. Efficacy of intrauterine Device in the treatment of intrauterine Adhesions.Biomed research International. Vol 2014,Article ID 589296 http//dx.dot.org/10.1155/2014/589296

Physical Barrier: Foleys Balloon

Foleys catheter with an inflated balloon is inserted into the uterus after adhesiolysis and kept in situ for several days after elimination of the adhesions. This causes the physical separation of the uterine walls in the initial days when fibrous bands of adhesions are more likely to develop. However the disadvantage of using Foleys catheter is patient requires longer

hospitalisation and the procedure is a bit painful and carries the risk of infection and cervical incompetence.

Keeping a ballon inside the uterine cavity and subsequent attempt to induce and encourage endometrial growth sounds a bit illogical short duration of treatment which in itself is an obstacle in ensuring definite results in preventing re adhesions [58]

Table 4 Showing the results of 168 women with IUA after lysis of Adhesions and insertion of Foleys Cather Balloon

	No. of women	Normal menses	Hypomenorrhea	Amenorrhoea
Comninos				
AC	50	35	5	10
Zourlas[53]				
Oneptto [54]	35	17	4	14
Klein[55]	11	10		1
Valsecchi[56]	21	14	6	1
Waniorek[57]	51	46		5
total	168	122(73%)	15(9%)	31(18%)

Reproduced from: Schenker[58] et al intrauterine adhesion; an updated appraisal fertility and sterility.Vol37 No.5 593-610

Intrauterine Balloon stent

A intra uterine stent was also described as mechanical method to prevent adhesions recurrence[58]. it is a silicon made triangular device which fits the normal triangular shape of the uterine cavity (cook medical Inc, Bloomington USA) With uterine stent the author reported among 1240 patients treated using intrauterine stents, preganancy rate of 61.6 % and spontaneous miscarriage rate of 6 %[59]. In a cohort retrospective study of 107 patients with AS, the use of intrauterine balloon stent compared with IUD and hyaluronic acid, resulted in significantly higher reduction of adhesion recurrence rate[60] although this encouraging evidence, data about its safety and efficacy seems still insufficient.

How ever in a randomised controlled trial comparing the efficacy of Intra uterine balloon and intra uterine device in prevention of adhesion re formation it was found that there was no significant difference in the incidence and the amount of adhesion re formation between the IUD group and intra uterine balloon group. [61]

Gel Barrier

Adhesion prevention adjuvents became available to practising gynaecologists since 1990 with the introduction of interceed Absorbale Adhesion Barrier (Gynaecare USA). Other site specific barrier followed including Preclude (Gore Tex USA) and Seprafilm Bio Absorbable membrane (Genzyme USA) [62].

Hyaluronic acid is one of the most widespread component in human tissue it is involved in many biological function such as mechanical support, cell migration, and proliferation. In the last decades products derived from hyaluronic acid have been adopted in gynaecologic surgery to prevent both intra peritoneal and intra uterine adhesion [63, 64, 65]

Hyaluronic acid generates a temporary barrier between organs which mechanically obstacles adhesions formation. In addition, these products influence peritoneal tissues repair by increasing the proliferation rate of the mesothelial cells [66]

Autocross linked hyaluronic acid (Hyalobarrier) It is a new anti adhesion barrier capable of preventing adhesions formation after gynaecological surgery [67]. It is a highly viscous gel formed by the auto cross – linked condensation of hyaluronic acid. A recent systematic review confirmed that it can prevent intra peritoneal adhesions by laparoscopic myo mectomy and intra uterine adhesions after hysteroscopic procedure [68]. In a randomised controlled trial of 84 women auto cross linked hyalorunic acid gel (hyalobarrier Gel FAB – Fidia advanced polymers, Abano Term Italy) was compared with no therapy after surgical treatment of Asherman syndrome. Post operative ultrasound studies demontrated that the walls of the uterine cavity remained separated for atleast 72 hours. At second look hystyeroscopy 3 months after the procedure IUAs were substantially reduced in patients receiving the adhesion barrier compared with the control group [69]. Auto cross linked hyaluronic acid may also be suitable for preventing IUAs because of high sensitivity and prolonged residency time on an injured surface[70].

Sepra film: The other anti adhesion barriers used are chemically modified hyaluronic acid sodium hyaluronate and carboxy methyl cellulose (seprafilm). A randomised controlled blind study was done on 150 patients who underwent surgical evacuation or curettage after missed or incomplete abortion. A subgroup of 50 patients was treated with seprafilm out of which 90 % were adhesion free at the end of 8 months. In another study Adhesions were found in (10%) women receiving treatment compared with 7 of 14 (50 %) in the control group who had not become pregnant [71].

Alginate carboxymethyl cellulose hyaluronic acid: A prospective randomisd trial including 187 case study was done on a brand new hyaluronic acid. Four weeks after sugery intra uterine adhesions were significantly lowered compared with carboxymethyl cellulose hyaluronic acid [72].

Oxiplex/AP Gel (Fzio Med, INC san Luis Obispo, CA): A formulation of viscoelastic gel was shown in preclinical studies to be most effective in reducing adhesions to peritoneal surfaces following surgery. It is a sterile non pyrogenic gel adjusted to isotonicity with Sodium Chloride[73]. It is a new intraperitoneal gelatineous compound that is composed of polyethylene oxide and carboxy methyl cellulose stabilised by calcium chloride. carboxy methyl cellulose decreases the injured tissue apposition required for adhesion formation[74]. This was supported by Sardo *et al* who worked on 110 patients diagnosed during office hysteroscopy as having single or multiple lesions suitable for surgical treatment or resistant dysfunctional bleeding requiring endometrial ablation[76].

In the mean while ferric hyaluronic acid is removed from the market for its toxicity found in 2003[77]

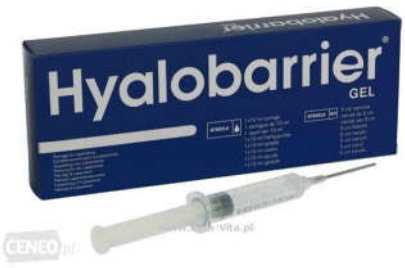

Fig 1 Hyalobarrier (Reproduced from http://novus-ms.com/en/hyalobarrier-gel-endo-2/)

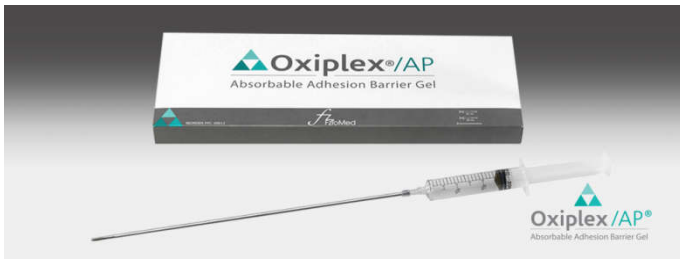

Fig2 Oxiplex /AP gel reproduced from (https://www.fziomed.com/products/)

Fig 3 Sepra film reproduced from (https://geosurgical.com/genzyme-4301-02-4301-02-wb10)

Group 2 Medical Therapy (Hormones and other medications)

Restoration of Normal Endometrium

In order to restore basal endometrium and rebuild the normal endometrial layer many workers have proposed hormonal treatment [78, 79, 80]. The general idea is to encourage fast growth of any residual endometrium immediately after surgery with dual purpose of preventing new scar formation and restoring a normal environment.

It is supposed that this goal can only be achieved with supra physiological hormonal level[81]. Wood and Pena introduced is the use of estrogens after lysis of adhesions[82]. Myer *et al* proposed a prolong pre operative and a post operative treatment with estrogens in 12 subjects which severe amenorrhea. All women resume a normal menstrual pattern and six of them became pregnant [83].

Post operative treatment with estrogen therapy (a daily oral dose of 2.5 mg conjugated equine estrogen with or without opposing progestins for 2 to 3 cycles [84, 85, 86,87].

No comparative studies were found which have been performed investigating dosage, administration or combination of hormones. One non randomised study reports that hormone treatment alone is as effective as hormone treatment and IUD in combination [88]. Many clinicians induce endo metrial growth with estrogen alone while others prefer estrogen in combination with progesterone. And there seem to be increasing agreement that estrogen therapy should be further utilised for treatment.

March *et al* suggested a treatment with micronized oestradiol 2 mg daily for 30 – 60 days and medroxy progesterone acetate 10 mg perday at last 5 days of oestrogen therapy 89 where as other authors prescribed estradiol valereate 4 mg per day for 4 weeks and medroxy progesterone acetate 10mg per day at last 2 weeks of treatment. [90 91]

Evidence shows that estrogen–progestin treatment after curettage for post partum hemorrhage or incomplete abortion also increases endometrial thickness. 60 women were randomised to receive estradiol valereate 2mg for 21 days and norgestero l 0.5 mg in the last 10 days of oestrogen treatment. after 21 days all women under went a transvaginal ultra sound. The endometrial thickness, width and volume were reported significantly elevated in the treated group. [92]

Steroids with or without promethazines have been prescribed postoperatively for a few days with good results [93]

Increasing the vascularity of the endo metrium

The use of sildenafil citrate intra vaginally was documented as possible pharmacologic treatment to restore endometrial thickness. This is type 5 specific phosphor-diesterase inhibitors that enhances vasodilator effect of the nitric oxide NO whose synthase isoforms were also found in the uterus. In a prospective observational study sildenafil citrate improved endometrial thickness in 92 % of cases who presented thin endometrium (thickness less than 8 mm [94]

A combination of oestradiol and sildenafil citrate improved endometrial blood flow and endometrial thickness in 4 women with prior failed assisted reproductive cycles due to poor endometrial response[95]

There are 2 case reports after use of sildenafil in AS. endometrial thickness significantly improves with treatment and both women were pregnant after the first treatment cycle [96]

Table 5 Pharmacological agents to prevent and or decrease adhesion formation:[97]

Pharmacological agents	Mechanism of actions	Human studies	
		Laparotomy	Laparoscopy
Anti inflammatory agents	Anti inflammatory action		
Steroidal agents	Anti inflammatory plus anti fibrinolytic actions	Rock *et al* (1984), jansen (1985), Querleu *et al* (1989)	Fayez and Schneider (1987)
Anti histaminics	Anti inflammatory plus anti fibrinolytic actions	Rock *et al* 1984, jansen 1985, Querleu 1989	Fayez and schneider (1987)
Progestogens	Anti inflammatory plus immunisuppressive properties	Eddy *et al* (1980) Maurer and Bonaventura 1983	
Anti coagulants heparins	Interactions with anti thrombin III in the clouding cascade or direct stimulation of the activity of plasminogen activator	Jansen (1988) Reid (1997)	Fayez and schineider 1987
Fibrinolytic agents Plasmin preparation Plasmin activators	Direct action : reduction of the fibrinous mass Indirect action : stimulation of plasminogen activator activity Prophylaxis against infections and hence the inflammatory response that triggers the adhesion formation	Jansen (1988) Reid *et al* (1997) Hellebrekers *et al* (2000)	Fayez and schineider (1987)

Reproduced from[97]: C nappi, A Sardo, E Greco, M Guida, S Bettocchi, G Bifulco. Prevention of Adhesions in Gynaecological Endoscopy Human Reproduction Update.2007 vol 13 No 4 pp 379- 394

Group 3: Regenerative Medicine and Stem Cell

Endometrial tissue has an intrinsic capacity of regeneration. endometrial regeneration normally occurs after menstruation and delivery. There is substantial vidence in literature that adult endometrial tissue contains epithelial progenitors cells and mesenchymal /stromal (MSC) cells [98]. these cells could be the target of a specific therapy in order to regenerate the endometrial tissue in cases of dysfunctional or atrophic endometrial. Recently a case report of a severe Asherman syndrome treated with autologous stem cells isolated from the womens own bone marrow has been reported [99]. The woman

has history of infertility and hypomenorrhoea following a D &C in 2005. She was treated hysteroscopically for severe intra uterine adhesions. and a Y shaped IUD was placed inside the uterus for six months. During this time,she also received therapy with combined estrogen and progesterone finally after failure of the hormonal therapy in restoring the endometrium, endometrial stem cells were were implanted inside the uterus after curettage on the second day of menstrual cycle. A clinical pregnancy was obtained after a heterologous embryo transfer.

A study done on cohort 16 patients age 30 to 35 with refractory Asherman syndrome and endometrial atrophy was done. In the study group patients were treated and delivered with Auto logous cell therapy with CD 133 + . This seems to improve the endometrial cavity in patient with refractory AS and Endometrial atrophy. conception attempts following reconstruction of the endometrium resulted in two spontaneous pregnancy 2 and 4 months after cell therapy and 7 positive preganancies after 13 embryo transfer resulting in 3 biochemical pregnancies and 2 misscarriages at 9 and 17 weeks, one ectopic preganancy and 2 ongoing pregnancies [100]
In another study done by Jichun tan *et al* on 7 infertile women between 20 to 40 yeras old diagnosed with severe AS grade 3 to 5 by hysteroscopy. Autologous menstrual blood derived stromal cells transplantation was conducted followed by HRT. Results showed that endometrial thickness was significantly increased to 7 mm in 5 women which ensured embryo implantation. 4 patients underwent FET and 2 of then conceived successfully. One patient has spontaneous preganacy after 3.5 months of transplantation. [101]

Irene C *et al* investigated the engraftment and proliferation of human bone marrow –derived stem cells in an animal model of Asherman Syndrome. This murine model confirms that these cells engrafts around endometrial vessels inducing proliferation of surrounding cells through paracrine molecules such as thrombospondin 1 and IGF 1. [102] This pioneering discoveries could open a new scenarios in the management of AS although more evidence are mandatory.

Group 4: Miscellaneous Approach

Second look hysteroscopy:

Valle and Sciarra reported a 50 % and 21.6 % of recurrence in severe and moderate AS respectively [103]. Timely recognition of any recurrence of adhesions is essential to provide the best prognosis, there fore it is necessary to repeat the surgery. For this reason most treatment protocols include a follow up to assess endo metrial restoration after surgery. If this is not done then there is increased obstetrics risk [104]. Although restoration of mens truation is good marker of success, other diagnostic investigations are fundamental for an exhaustive evaluation. Presently post operative assessment of the uterine cavity is done one to two months after the surgery [105].

Fernandez *et al* concluded that after treating 23 women who had AS 20 had three separate procedure to treat the adhesions and rest needed higher order procedure at the conclusion of the treatment more than 80 % of the women had either no adhesions at all or only mild adhesions. So he concluded that number of hysteroscopic procedure envisioned to treat AS should not be a limiting factor. He also concluded that it is appropriate to treat women especially those who are younger than 35 years until uterine anatomy permits the visualisation of both the ostias. [106]

Oral mucosal sheet

A study done by Kuramoto G *et al* to assess the efficacy of oral mucosal epithelial cell sheets (OMECS) in treatment for intra uterine adhesion. It was found that non treated specimen at 1, 2 and 8 days after surgery did not show any uterine cavities typically caused by intrauterine adhesions in contrast to the histology of uterus transplanted with OMECS immediately after endometrial damage. It showed the presence of uterine cavities and further more stratified squamous cells on the luminal surface.[107]

Platelet Rich Plasma

Zhang *et al* had shown that plate rich plasma is an auto logous blood product which contains abundant growth factors, which can significantly enhance the Menstrual stem cell proliferation and stemness in vitro. They explored the feasibility of co transplantation of PRP and MenSC in Ashermans syndrome treatment and observed magnified therapeutic effect. co transplantation with PRP significantly increased the level of IL 1 beta, IL4, and IL 10 in the injured uterus [108].

DISCUSSION

The major cause for infertility and menstrual disorder in a female is recognised as intra uterine adhesions. Good surgical techniques combined with adhesions barriers has demonstrated the potential for prevention for further adhesion formation.

Available data and evidence shows some improvement with different approaches. The following consensus can be reached taking into account with strong and weak evidences.

For IUA division it is better to minimise the electrical instrumentations when ever possible. Mono polar cautery is particularly responsible for initiating more post operative adhesions.cold scissor, laser and morcellation is better[109]

As per physical barrier are concerned the IUD could be applied after hysteroscopic adhesiolysis to avoid regeneration of IUAs. It seems that IUD needs to be combined wit other ancillary treatments such as hormone therapy Foleys catheter, hyaluronic acid gel or amnion graft to obtain maximal out comes,particularly in patients with moderate to severe adhesions.

Placement of an IUD to maintain the uterine cavity is safe and effective in ensuring the return of normal menstruation and later pregnancies with minimal complications.

Several studies reported different postoperative outcomes after using the IUD, however no comparative studies have confirmed the ideal IUD, duration course of IUD therapy and the combination of IUD [110]

Regarding Gel barriers Instillation of hyalo barrier gel may have a beneficial effect after hysteroscopic myomectomy or adhesiolysis. The efficacy of the adhesive gels are extensively studied and they are further evaluated and shows promising results in reducing the recurrence of the adhesions. Further evaluation is necessary to confirm their benefits. Re evaluation after one to two weeks post operatively may show early identification of the recurrent adhesions while small adhesions allow resection before these adhesions further worsen. [111]

As per hormones and medications are concerned post operative hormone treatment using estrogen with or without using a progestin may reduce the recurrence of IUA

Use of estrogen around 2mg two tablets perday after adhesiolysis is beneficial [112].

Medications to improve vascular flow to the endo metrium should be used carefully and should not be used outside the ambit of rigorous research protocols.

There is no evidence to support or refute the use of preoperative, intra operative or post operative antibiotic therapy in surgical treatment of IUA[113].

Experimental protocols to rebuild the endo metrium by infusing the stem cells derived from the patients may provide some promises in the future. There is substantial evidence in literature that adult endometrial tissue contains epithelial progenitor cells and mesenchymal stromal cells. These stem cells may be derived from the patients blood cells, bone marrow or endometrial tissue how ever further long term studies are needed to confirm the safety, efficacy and risks associated with these protocols. These pioneering discoveries could open a new scenario in the management of AS although more evidences are mandatory [114].

Evaluation of of uterine cavity after adhesiolysis is an important step in AS manage ment. Complete resolution of the adhesion is not always possible with a single procedure especially in severe stages where a high recurrence is documented [115].

Ultrasound, HSG and hysteroscopy are the most common follow up methods. USG is an cost effective tool for measuring endometrial thickness and for evaluation of normal endometrial development during menstrual cycle[116].

HSG has the advantages to check the tubal patency and at the same time it can help in the resolution of thin adhesions from pressures of the liquid contrast medium.

Hysteroscopy how ever remains the only method which allows an accurate estimation of adhesion recurrence and it is most commonly used in clinical practice. it also allows in office adhesiolysis[117].

CONCLUSION

It has been observed over last few decades that incidence of intra uterine adhesion or Asher man Syndrome is steadily increasing. Trauma to a pregnant uterus especially after missed abortion is identified as main offender followed by intrauterine surgery for myomas. The syndrome is mostly expressed by menstrual disorders like amenorrhoea or hypo menorrhoea followed by sub fertility. Pregnancy when achieved may be complicated by premature labour, placenta previa and placenta accrete. The introduction of hysteroscopy has improved the fertility outcome and the treatment success rate In spite of different mode of treatment, recurrence rate of adhesion is found to be very high and we must continue to look for the techniques which reduces the formation of new adhesions. Various modes like IUD, uterine stent, adhesion barriers and hormonal treatment have proven efficient yet more comparative researches are needed to optimise the next treatment after initial hysteroscopic approach to women with AS. Multiple approach combining with best available evidence to date achieves the greatest result for the prevention of reappearance of adhesions in the post operative management of AS [118].

A novel approach based on endometrial stem cells and the understanding of physiopathology mechanism involved in endometrial regeneration could represent a worthwhile area for a further research. Currently the use of word catheter filled with 3 -4 ml of saline, previous instillation of intrauterine hyaluronic acid viscous elastic gel, short term antibiotic treatment and concurrent hormonal therapy for at least 21 days ideally 2 cycles and posterior second look hysteroscopy control at 2 months have shown to be best combination for current management of prevention of further adhesion formation [119].

Abbreviations

IUA: Intra Uterine Adhesion AS: Asherman Syndrome

Competiting Interest*:* The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors Contribution

P BJ has reviewed the literature and prepared the manuscript, M R gave an important contribution in revising text and A I significantly contributed to revise the article.

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