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RESEARCH ARTICLE

REVISITING DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN ASHERMAN'S SYNDROME: A RETROSPECTIVE ANALYSIS OF 5 YEARS

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ABSTRACT

Aim: To Analyse the Etiologies, clinical features, diagnostic modalities used and the therapeutic outcome following Hysteroscopic adhesiolysis among women with Asherman's Syndrome, managed at our Hospital during 5 years (1st March 2013 to 31st March 2018). **Material and Methods:** A Retrospective Cross sectional Study of 5 years was conducted and those Women who had undergone Hysteroscopic adhesiolysis for Asherman's syndrome were selected. Case records of these women were retrieved from Medical Record Department. Sociodemographic, clinical, Obstetric profile, Hysteroscopic findings, details of adhesiolysis, changes in menstrual pattern and Fertility outcomes were recorded. **Results:** The leading cause for Asherman's was D&C (62%) and followed by Tuberculosis (19%).TVS assessment of Endometrial thickness was 64% diagnostic for moderate Asherman's, if there is thin ET with few echogenic shadows and Doppler flow is impaired *and* irregular, echogenic ET (<2 mm) with High resistance doppler flow is diagnostic for severe Adhesions in 87.5%($p<0.001$). Myometrial thickness assessement called RR **method** (named after authors) guided the amount of adhesiolysis and none of our women required laparoscopic assisted hysteroscopic adhesiolysis. Repeat Second look Hysteroscopies carried good results, 100% adequate cavity and menses restoration occurred after second look Hysteroscopies. Conception rate was 38% and term Pregnancy rate was 67%, majority of conception occurred in severe adhesion group. Obstetric complications can occur following adhesiolysis. Role of IUCD vs Foleys and E+P vs E+P with stem cell instillation were equally efficacious. **Conclusion**: skilled Hysteroscopy is the Gold standard for diagnosis and treatment of Asherman's syndrome

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INTRODUCTION

Asherman's Syndrome is the condition that occurs when scar tissue is formed inside the uterus and or cervix. It leads to variable degree of scarring and causes menstrual disturbances, infertility, and relatively rare Placental abnormalities like Placenta accreta and previa (Deans, 2010). Heinrich Fritschin1894, first published article on amenorrhea associated with intrauterine adhesions in a Patient after postpartum curettage. Intrauterine adhesions also known as synechiae, that occurs in 1.5% of women undergoing Hysterosalpingography (Coccia, 2008; Chen *et al*., 2017).

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Pregnancy is the most common predisposing factor, usually associated with trauma to the endometrium, as seen in patients undergoing curettage during Puerperium, missed abortion, evacuation of a hydatidiform mole, Myomectomy or cesarean section (Chen *et al*., 2017). Any Infection of the endometrium that leads to severe chronic inflammation can develop intrauterine adhesion example intrauterine devices, Genital tuberculosis, Schistosomiasis and even obesity can develop adhesions even without uterine surgeries. Hysterosalpingography (HSG) is the useful screening modality for intrauterine adhesions having 75% sensitivity and 95% specificity (Amin *et al*., 2015; Hooker *et al*., 2016). Transvaginal Ultrasonographic (TVS) examination is 95% specific with low sensitivity for the diagnosis of adhesions but an important tool for planning Hysteroscopic adhesiolysis. Adhesions are best visualized in the luteal phase of the menstrual cycle and appear as an echogenic, irregular eccentric lines within the endometrium or as a focal narrowing of the endometrial thickness (Amin *et al*.,

2015; Hooker *et al*., 2016). Hysteroscopy is the current method of the choice for diagnosing, treating, and following the Patients with Asherman's syndrome (Management of Asherman's syndrome, 2012; Myers, 2012). Despite the wide use of diagnostic and Operative Hysterscopy, the management of Asherman's Syndrome is still challenging.

Aim: To Analyse the Etiologies, clinical features, diagnostic modalities used and the Therapeutic outcome (Restoration of menstrual functions, Conception rate, live pregnancy rates) following Hysteroscopic adhesiolysis among women with Asherman's Syndrome, managed at our Hospital during 5 years (1st March 2013 to 31st March 2018).

MATERIALS AND METHODS

A Retrospective Cross sectional Study of 5 years from1stMarch 2013 to 31st March 2018 was conducted at our Hospital. Operation Theatre (OT) notes were referred and those Women who had undergone Hysteroscopic adhesiolysis for Asherman's syndrome were selected. Case records of those women were retrieved from Medical Record Department and were also telephonically contacted for the complete information. Information regarding socio-demographic, Obstetric and menstrual profile, clinical features, various etiologies, diagnostic modalities (haematological, hormonal, Pathological, Radiological) Hysteroscopic findings, details of adhesiolysis, changes in Menstrual pattern and Fertility outcomes were recorded.HSG is not done in our hospital, preoperative diagnosis was considered mainly by the history of Hypomenorrhea / amenorrhea, Transabdominal and Transvaginal Ultrasonographic findings with normal hormonal profile. We have coined the term "**RR method**" (named after main author's names), this refers to the measurement of myometrial thicknesses at fundal, anterior and posterior walls that guided the amount and the direction of Hysteroscopic adhesiolysis lateral and metroplasty. Routine Lap assisted adhesiolysisis not done in our Hospital. Office BETOCCHI Hysteroscope (2.9 mm diameter, 30 degree telescope with an operative sheath) was used and Hysteroscopy with Vaginoscopic approach was done.Saline was used as the distending medium. Asherman's was graded according to MEC (Manchanda's Endoscopic Centre) classification for Asherman's Syndrome (Sravani Chithra *et al*., 2016). Adhesiolysis was done by using 5 Fr scissors.

Postoperatively Endometrial tissue was sent for Histopathological examination and TB-PCR. Multiload 375 A Copper T without copper wire or 14 Fr Foley's urinary catheter with bulb inflated with 3ml saline was introduced into the endometrial cavity to act as a mechanical barrier for adhesion prevention.SimultaneouslyConjugated estrogen for 21 days andMedroxy progesterone acetate for 7 days *(dosage according to the severity of AS)* or E+ P and stem cell instillation was done to enhance epithelisation and endometrial growth (Table 1). All the women were followed up and Second look hysteroscopy was scheduled after their 1st menses or 1 month whichever is earlier. If adhesions were found, adhesiolysis was done and Relook hysteroscopy was again scheduled after 4 weeks, till the restoration of normal cavity for conception or restoration of menses (as per patient's need) .Necessary informations were obtained from Case Records and also from telephone.

RESULTS

Total 28 women enrolled for the study, but 7 women were excluded as 2 women had incomplete information in the case records and 5 were lost to follow up. So finally 21 women were considered. Majority 9 (42.5%) women belonged to 30 to 35 years of age groups. 43% were multiparous and 57% were nulliparous (Table 3). Most common complaint was Menstrual Disturbances, occurring in all 21 (100%) women while infertility along with menstrual disturbances occurred in 16 (76%) women. Common etiologies were Dilatation and curettage done for evacuation of uterus and Genital Tuberculosis (Table 4). As per MEC grading, 2 (9.5%) women were classified into mild,11(52.4%) moderate and 8 (38.1%) severe Asherman's on first hysteroscopy (Fig.1)

All 13 (100%) women with hypomenorrhea had restored their normal menses while 5 (62.5%) amenorrhic women resumed their mensesafter first adhesiolysis (Table 5). On Relook Hysteroscopy, 6 (28.6%) women with normal uterine cavity and 9 (42.9%) with mild adhesions were excluded form repeat Hysteroscopy. 6 Women having normal menses but are infertile were subjected for 2nd relook hysteroscopy for adequate cavity restoration. None of the cases required Laparoscopic assisted Hysteroscopic adhesiolysis. Simultaneous diagnostic Laparoscopy was done in 16 Infertile Women for assessing tubo-ovarian or any abdominal pathology (Table 6). Preoperative TVS and Doppler flow revealed that thin ET with few echogenic shadows andimpaired Doppler flow was diagnostic of moderate Asherman's in 7 (63.6%) women, while irregular thin echogenic ET with high resistance to Doppler flow was diagnostic of severe Asherman's in 7 (87.5%) women (Fig 2, Table 7).

Histopathological examination showed that all women with mild adhesion and 72% with moderate adhesion had secretory endometrium. Granulomatous endometritis was seen in 38% of severe adhesions (Fig 3). Comparison of different Mechanical barriers ie. Multiload 375 A IUCD vs Foley's catheter, which were used for prevention of adhesions did not reveled any statistically significant difference.Comparison of estrogen and progesterone vs E+P with stemcell instillation for promotion of endometrial growth were equally efficacious (Table 8) Total 8 (38%) women had conceived,among which 50% in mild group, 36% moderate and 37.5% in severe group. Term pregnancy rate was 67%, among which 25% delivered vaginally and 75% by caesarean section. One woman P2L0 in severe adhesion group underwent Preterm LSCS followed by Peripartum hysterectomy at 32 weeks for placenta percreta **(**Table 9).

DISCUSSION

There is a wide spectrum of uterine syneche or adhesions in terms of severity and location. It could be thin, filmy, diffuse, broad to dense, thick and fibrous bands that ultimately obliterates the cavity. Adhesions may arise from endometrium, myometrium and connective tissue. Adhesions arising from endometrium are thin and easily lysed while adhesions from myometrium are more common and are thick with overlying thin basalis layer of endometrium from which new endometrium grows. Connective tissue adhesions are dense with no overlying endometrium and have worst prognosis (Sravani Chithra *et al*., 2016).

Table 1. MEC (Manchanda's Endoscopic Centre) Classification of Asherman's Syndrome[8]

Grade 1	*Mild*	Less than 1/3rd of uterine cavity obliterated (flimsy / dense adhesions)
Grade 2	*Moderate*	1/3rd to 2/3rd of uterine cavity obliterated (flimsy / dense adhesions)
Grade 3	*Severe*	More than 2/3rd of uterine cavity obliterated (flimsy / dense adhesions)

Table 2 Dosage of conjugated estrogen and medroxyprogesterone acetate according to severity of AS[8]

Grades of AS	Conjugated estrogen (21 days)	Medroxyprogesterone acetate (7 days)
Mild AS	0.625 mg BD	10mg BD
Moderate AS	1.25 mg BD	10 mg BD
Severe AS	1.25 mg QID	10mg BD

Table 3. Socio-demographic Profile

Age distribution	
20 – 25	1 (4.8%)
25 – 30	5 (23.8%)
30 -35	9 (42.9%)
>35	6 (28.6%)
Total	**21**
Parity	
Nulliparous	12 (57%)
Multiparous	9(43%)

Table 4. Complaints and Causes of Asherman's Syndrome

Complaint	
1.Menstrual Disturbances	19 /21
-Hypomenorrhea	12 (57.1%)
-Amenorrhea	7 (33.3%)
-Normal Menses	2 (9.5%)
2.Infertility	16 /21
-Primary	5 (23.8%)
-Secondary	11 (52.4%)
Causes of Asherman's Syndrome	4 (19%)
-TB	13 (61.9%)
-History of D& C	5
Abortion	8
RPOC	2 (9.5%)
-LSCS	1
History of PPH – compression sutures	1
LSCS with no complications	2(9.5%)
No cause	

Table 5. Adhesiolysis and correction of menses

Hysteroscopic Adhesiolysis (Attempts)	Hypomenorrhea (n=13)	Amenorrhea (N= 8)
1st Adhesiolysis	All 13 women (100%) restored Normal menses	3 (37.5%) restored Normal menses 5 (62.5%) resumed menses
2nd Adhesiolysis	-	100% restoration of Normal menses

Table 6. Adequate Restoration of cavity in relation to Repeat (Second look) Hysteroscopies

Severity of adhesions	Hysteroscopic adhesiolysis 1st attempt	2nd attempt (1st Relook)	3rd attempt (2nd Relook)	4th attempt (2nd Relook
Normal	0	**6** (28.6%) Excluded 9 (42.9%) Excluded – normal menses & fertile	4 Excluded	1 (%)
Mild	2 (9.5%)		1 Excluded	0
Moderate	11(52.4%)	4 (19.0%) 2 (9.5%)	1	0
Severe	8 (38%)		0	0
Total	21	21	6	1

Table 7. Preoperative TVS & Doppler flow

ET	Mild	Moderate	Severe	P Value
Normal ET &dopplerFlow normal	2 (100%)	1 (9%)	0	p= 0.01
ET Thin< 6&Flow normal	0	3 (27.2%)	0	p= 0.01
ET Thin, few echogenic shadows &Flow impaired	0	7 (63.6%)	1(12.5%)	P< 0.001
ET Thin (<2mm) irregular echogenic High resistance doppler flow	0	0	7(87.5%)	P< 0.001
Total	2	11	8	

Table 8. Comparison of different Mechanical barrier and Drugs

1.Mechanical barrier (Prevention of adhesion)	Total no. women n (%)	Adhesion Reformation n (%)	Patient's satisfaction
•Multiload 375 A without copper wire	16 (76%)	11 (52%)	p = 0.01 NS, Satisfied
•Foleys Catheter	5 (24%)	3 (60%)	p = 0.15 NS, Unsatisfied, Cumbersom
Different drugs (for Endometrial regeneration)	Total no. women n (%)	TVS - ET	p - value
E + P		6.2 +_ 1.2mm (range 6-8 mm)	P= 0.01, NS
E + P & Stem cell instillation	17 (81%)		
	4 (14.2%)	7.1=_ 3.3mm (range 6.5- 9mm)	P= 0.00, NS
Total	21		

Table 9. Pregnancy outcome n = 8 (38%)

Pregnancy outcome	N (%)	Grades of Asherman's
1st Trimester spontaneous abortion	2 (25%)	Mild
Ectopic Pregnancy/ Molar	1 (17%)	moderate
Preterm LSCS – 32 weeks (Complete accreta)	1 (17%)	Severe
Term Pregnancy	4 (67%)	
▪ NVD	1 (25%)	Moderate
▪ LSCS	3 (75%)	severe

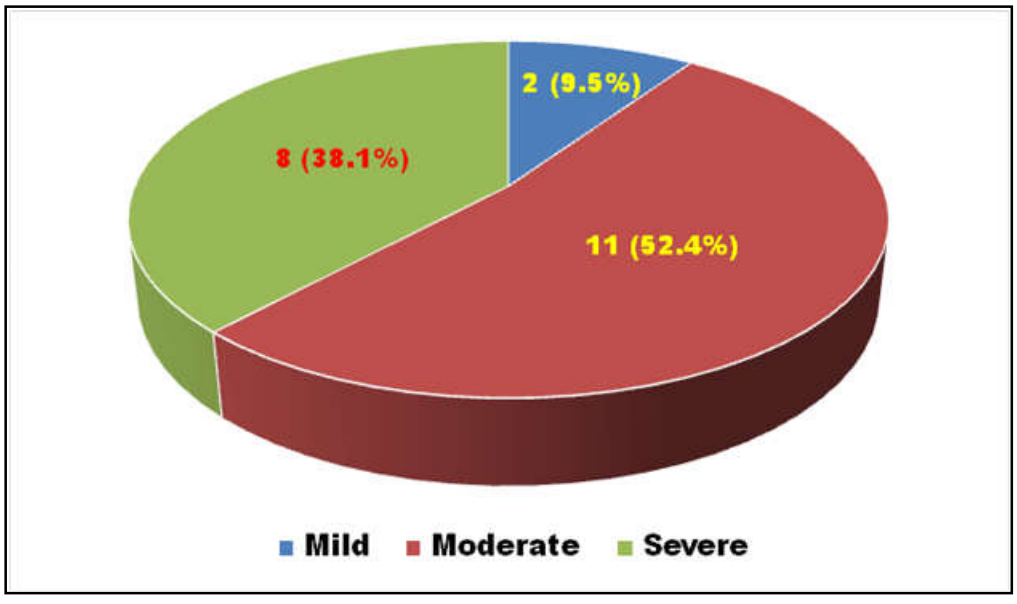

Fig.1. Grades of Asherman's Syndrome

The menstrual and fertility outcome following adhesiolysis is challenging. Yamamoto N *et al* reported that prior history of D and C was the leading cause of Asherman's, that occurred in 77% of these women. No complication occurred due to hysteroscopic adhesiolysis. Adhesion recurrence rate was 15% and second hysteroscopic adhesiolysis procedure was done on these women (Nari Yamamoto Reiko Takeuchi, 2013). Similarly in our study also no complications occurred due to adhesiolysis. Few adhesion reformation had occurred, but it did not increase the severity of AS.

A study conducted by Bhandari *et al* reported that 50% of hypomenorrhic women and none of amenorrhic women had restored normal menses after adhesiolysis, however 62.5% of amenorrhic women had resumed menses. Laparoscopic assisted adhesiolysis was performed in 70% of the patients (Shilpa Bhandari *et al*., 2015) [10]. Present study showed that all hypomenorrhic women had restored normal menses after first adhesiolysis and all amenorrhic women had also restored normal menses after second adhesiolysis.

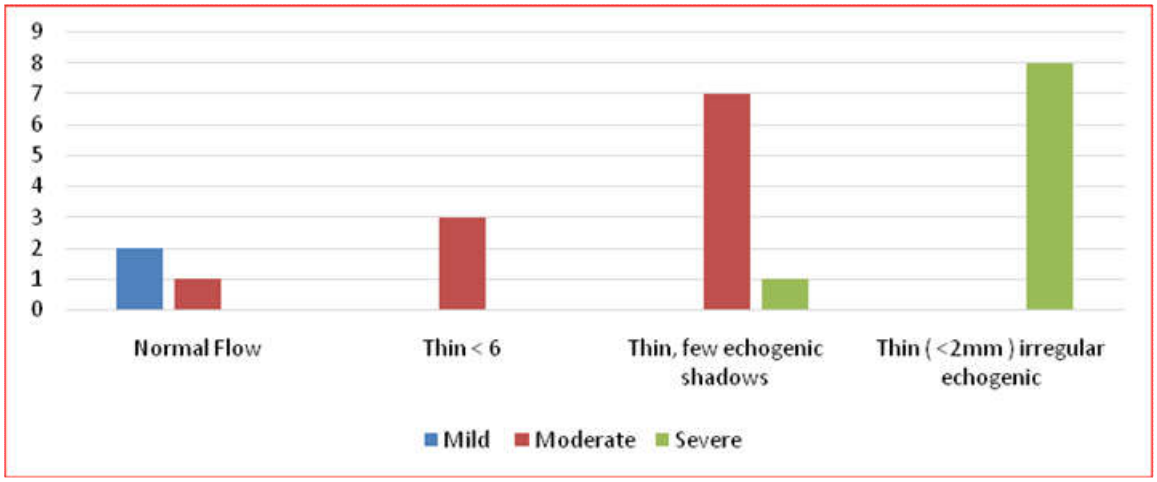

Fig. 2. Preoperative TVS & Doppler flow *[Endometrial thickness &doppler flow]*

Fig 3. Histopathology of Endometrial tissue

Histopatholoy	Mild adhesion	Moderate	Severe
Secretory	2 (100%)	8 (72.7%)	0
Atrophic	0	2 (18%)	2 (25%)
Granulomatous	0	1 (9%)	3 (37.5%)
Inadequate	0	0	2 (25%)
Total	2	11	8

We employed RR method and hence none of our women required Laparoscopic assistance. Various factors that can affect conception rates after hysteroscopic adhesiolysis have been reported, including adhesion severity, menstrual patterns after surgery and adhesion reformation after surgery. Yamamoto *et al* observed that out of 16 infertile patients, 9 conceived. 4 patients achieved term deliveries. None of the patients had obstetric complications. Two patients had spontaneous abortions, one had an ectopic pregnancy, one had an abortion at 16 weeks' gestation due to cervical incompetence, and one had a molar pregnancy and required uterine artery embolization for uncontrolled hemorrhaging during a dilatation and curettage procedure. Our study found 38% conception rate and 67% term delivery rate. One women developed Placenta accreta and hence peripartum hysterectomy was done at 32 weeks. The placement of an IUCD acts as temporary mechanical barrier and hasbeen considered the standard method for maintaining the uterine cavity after adhesiolysis, however different studies preferred different duration courses of IUCD such as 1, 2, and 3 months. But specific type and duration course to be used for this purpose remain a controversial issue. After hysteroscopicadhesiolysis the healed process occurs, with 96% of the women completing their wound healing within 2 months and subsequently endometrium reepithelization, or after hormone treatment to stimulate the endometrium and promote reepithelization. Roy *et al*[13]. showed that the conception rates in women with Uterine adhesions, depends upon on the stage of adhesions, which was 64.7% in mild adhesions, 53.6% moderate adhesions, and 32.5% with severe adhesions. They also reported a decreasing live birth rate from mild to severe adhesions (mild 94.4%, moderate 83.3%, and severe 66.6%). Yu *et al* also reported t the similar conception rates in women with mild, moderate, and severe adhesions were 64.7%, 53.6%, and 32.5%, respectively[14]. Our study found that live term pregnancy occurred more in moderate to severe adhesions, probably because majority of these women must be having myometrial adhesions rather than connective tissue adhesions. Repear second look Hysteroscopy is mandatory to achieve optimal outcome.

Summary

Present study also observed that most Common complaintwas menstrual disturbances (90.4%)andInfertility (76%).

- The leading cause for Asherman's was DandC (62%) and followed by Tuberculosis (19%).
- TVS assessment of Endometrial thickness was 64% diagnostic for moderate Asherman's, if there is thin ET with few echogenic shadows andDoppler flow is impaired.However ET (<2 mm) is irregular, echogenic with High resistance doppler flow is diagnostic for severe Adhesions in 87.5%($p<0.001$).
- Myometrial thickness assessmentguided the amount of adhesiolysisand none required Lap assisted hysteroscopicadhesiolysis
- Repeat Second look Hysteroscopies carried good results,100% Adequate cavity and menses restoration occurred after second look HysteroscopiesConception rate – was 38% and Term Pregnancy rate was 67% (mainlyamongmoderate – Severe adhesions)
- Adhesion reformation occurred but it did not advance the Asherman's grades.
- IUCD vs Foleys and E+P vs E+P with stem cell instillation were equally efficacious.

Conclusion

The leading cause for Asherman'sis D and Cdone for abortion or RPOC. Second look or Repeat Hysteroscopy is important for adequate cavity and menstrual function restoration .RR method (Preoperative Myometrial thickness assessment) is an important tool for guiding the amount and direction of adhesiolysis and thus the need for Laproscopic assisted Adhesiolysis be avoided. Pregnancy outcomes are challenging following adhesiolysis in Severe Adhesions.

Recommendation

We recommend that blind DandC for evacuation of RPOC should be strictly avoided. Hysteroscopy can be the choice forthe diagnosis and treatment of RPOC. Alternative measures can also be used like use of Mifepristone and Misoprostol or USG guided DandC with blunt curette only or Suction and Evacuation. Proper Patient counselling should be done, regarding repeat Hysteroscopy and also Gynaecologists should not be hesitant for relook Hysteroscopies. Pregnancy complications including Placenta Accreta can occur following adhesiolysis, so closely supervised Pregnancy at Tertiary care Hospital is recommended.

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