

Association of Endometrial Polyps with Membranous Adhesions in Uterine Cavity

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ABSTRACT : The membranous adhesions could induce implantation failure despite transplantation of high quality of embryo. Clinically, of the patients who have membranous filmy adhesions, endometrial polyps have been found in not infrequently. Thus this study was tried to evaluate the features of endometrial polyps and the effect of endometrial polyps on formation and extents of membranous adhesions in uterine cavity of infertile patients under hysteroscopy. A retrospective study was conducted on 34 infertile patients who were diagnosed as endometrial polyps with membranous adhesions during hysteroscopy from July 2008 to July 2011. Number, size, location and morphologic type of endometrial polyps were investigated. If needed, methylene blue solution was instilled to endometrial cavity to identify membranous adhesions. Then, associations between membranous adhesions with features of endometrial polyps were evaluated. Mean size of endometrial polyp was 1.6±0.6 cm, the bigger of endometrial polyps was, the larger of extents of membranous adhesions. ($p<0.05$). Endometrial polyps were locate evenly in endometrial cavity as follows: anterior uterine wall, 39.1%; posterior uterine wall, 34.8%; lateral uterine wall, 26.1%; upper: 29.4%, middle: 32.4%, lower segment, 35.3%. Mean number of endometrial polyps was 2.26±1.3. The pedunculated type was 37.7% and sessile type was 32.4%. There was no statistically significant association of location, number and morphologic type of endometrial polyps with membranous adhesions. In conclusion, hysteroscopy before *in vitro* fertilization on infertile patients was worthy because of removing of endometrial polyps and membranous adhesions.

Key words : Endometrial polyp, Membranous adhesions, Hysteroscopy

INTRODUCTION

Endometrial polyps are a common gynecologic condition which was estimated to be as high as 25% (Sherman et al., 2002). They are localized tumors in the uterine mucosa made up of glands and stroma around a vascular axis of one or more spiral arteries. Most endometrial polyps arise from the fundal or corporeal region and extend toward the internal OS. They may be single or multiple, measuring from a few millimeters to centimeters, and may be sessile

or pedunculated (Peterson & Novak, 1956; Savelli et al., 2004).

No definitive cause of endometrial polyps is known, but they appear to be affected by hormone levels and grow in response to circulating estrogen (Valle, 1980). For patients with endometrial polyps, abnormal uterine vaginal bleeding occurs in approximately 68% of cases and is the most common presenting symptom (Golan et al., 2001). Although bleeding is a common presentation, women with endometrial polyps may remain symptom free or present with this incidental finding on imaging for other indication (Wu et al., 2001). In reproductive women, endometrial polyps are associated with infertility, although the causal relationship remains uncertain (Taylor et al., 1992). Diagnosis can be

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made using transvaginal ultrasonography, hysterosalpingogram or hysteroscopy. Of them, hysteroscopy is the most sensitive of all diagnostic evaluations (Allahbadia & Sheth, 1996; Bingol et al., 2011).

Shin et al. reported the membranous filmy adhesions for the first time (Shin, 2010). In uterine cavity, they were attached to endometrium loosely or sometimes tightly. These membranous adhesions were stained by methylene blue solution, so it made it easy to be found by hysteroscopy. They also showed that removal of these membranous adhesions could increase the pregnancy rates. Membranous adhesions were confirmed as collagen matrix in tissue pathology. Also they were thought to be related with inflammation. They suggested that these membranous adhesions act as barrier to implantation of embryo (Shin, 2010).

Of the patients who have membranous filmy adhesions, endometrial polyps have been found in not infrequently. However, the association endometrial polyps with the membranous adhesions have not been studied yet.

The aim of the study was to evaluate the features of endometrial polyps in infertile patients by hysteroscopy. We also tried to analyze their association with membranous filmy adhesions.

MATERIAL AND METHODS

1. Patients Characteristics

From July 2007 to July 2011, 34 patients who were diagnosed as endometrial polyps and membranous filmy adhesions by hysteroscopy were recruited (Table 1) at Gangnam CHA medical center. Patients' criteria included age, gravida, parity, duration of infertility and previous tried number of in vitro fertilization (IVF). Also we investigated whether patients were pregnant or not after the procedure. Their mean age (\pm SD) was 35 ± 4 (29-37) years, the duration of infertility was 3.7 ± 2.8 years. The number of IVF before hysteroscopy was 1.9 ± 1.8 . From the infertility factors of view, tubal factors were 7 patients, male factors were 4 cases and unexplained cases were 23.

2. Endometrial Polyps: Location, Number, Size, and Morphologic Type

The location of endometrial polyps was defined by their roots, vertically as three equal parts: upper, middle, lower, simultaneously anterior, posterior, lateral by fundal dome and utero-tubal junction (Fig. 1). Endometrial polyps were categorized 1, 2 and multiple. Among their location, the main occupied lesion was analyzed. Multiple polyps were defined as the three or more polyps. Size was measured by transvaginal ultrasound and hysteroscopy. If endometrial polyps were more than one, total measured size was added. They were classified as pedunculated and sessile type by their morphology.

3. Extents of Membranous Adhesions

While examining hysteroscopy, membranous adhesions could be found using methylene blue solution (Methylene blue Inj. 1%[®], Jtpharm, Korea). The extents of membranous adhesions were calculated as percentage over whole endometrial cavity. The site of endometrial polyps was excepted from the analysis.

4. Hysteroscopy

Patients had the procedure in midproliferative phase. 100 μ g of misoprostol was inserted through vagina a day before the procedure. After the patients were IV general anesthetized, they were placed in dorsal lithotomic position and draped. After cervical dilatation, the hysteroscopy (30

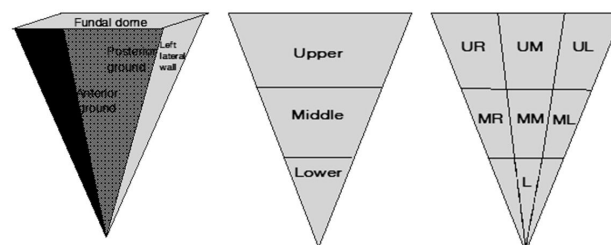


Fig. 1. Mapping of endometrial cavity. EM cavity was divided vertically as three equal parts: upper, middle, lower, simultaneously anterior, posterior, lateral by fundal dome and utero-tubal junction.

Table 1. Patient's characteristics

No. of subjects	Age	Gravity	Parity	Infertility factor	Duration of infertility (months)	No. of Prev. IVF
1	36	2	0	unexplained	40	1
2	27	1	0	tubal	46	0
3	36	0	0	unexplained	96	1
4	36	1	0	male	60	3
5	43	2	0	tubal	48	3
6	37	6	0	unexplained	30	0
7	35	0	0	unexplained	18	1
8	37	1	0	unexplained	36	2
9	34	1	0	unexplained	60	1
10	30	0	0	unexplained	36	2
11	33	2	0	male	16	2
12	40	4	1	unexplained	20	1
13	50	1	0	tubal	18	0
14	32	0	0	unexplained	45	2
15	28	0	0	unexplained	12	0
16	37	1	0	unexplained	180	3
17	38	0	0	male	60	2
18	32	0	0	unexplained	12	0
19	29	0	0	tubal	60	1
20	34	0	0	unexplained	60	1
21	45	2	0	unexplained	84	0
22	36	1	0	unexplained	12	0
23	38	2	1	male	60	9
24	38	1	1	unexplained	84	2
25	28	0	0	unexplained	24	4
26	34	0	0	unexplained	38	1
27	45	1	0	unexplained	26	6
28	39	0	0	tubal	18	0
29	31	0	0	unexplained	19	0
30	34	1	0	unexplained	60	1
31	35	2	2	unexplained	53	3
32	31	0	0	tubal	72	1
33	38	1	1	unexplained	12	2
34	33	1	0	tubal	58	3

Degree, 2.9 mm, Karl Storz[®], Tuttli-gen, Germany) was guided into the uterine cavity, and the cavity was systematically inspected for any abnormal findings. If abnormalities such

as polyps, membranous adhesion or septum were found, they were removed by forceps and/or scissor forceps. Hartman solution was used as an insufflations media.

If membranous adhesions were suspected, 6cc of methylene blue solution (Methylene blue Inj. 1%[®]) was instilled with 1:1 mix to saline. About 3-5 minutes later, stained lesions were checked by hysteroscopy. After removing these lesions using spoon forceps and biopsy forceps (CLICK'line[®], Karl Storz), tissues were sent to pathology.

5. Statistical Analysis

All analyses were performed with the SPSS Windows Release 12.0 software package (SPSS Inc., Chicago, IL, USA). Associations of location, number, and morphologic type of endometrial polyps to membranous adhesion were performed with the Kruskal-Wallis test and Mann-Whitney U-test, and association between size of endometrial polyps and extents of membranous adhesions was performed with Spearman's correlation test. Associations were considered statistically significant at P -value <0.05 .

RESULTS

1. Features of Endometrial Polyps

In 12 cases, one polyp was found and 10 patients had 2 polyps. The others, 12 patients have multiple endometrial polyps (Table 2). The average size of endometrial polyps was 1.6 ± 0.6 cm with the largest one was 2.5 cm. Pedunculated type was 23 cases and sessile type was 11 cases. Endometrial polyps were located evenly through uterine cavity as follows: anterior uterine wall, 39.1%; posterior uterine wall, 34.8%; lateral uterine wall, 26.1%; upper: 29.4%, middle: 32.4%, lower segment, 35.3%.

2. Association of Membranous Adhesions with Endometrial Polyps

Mean extents of membranous adhesions in patients with endometrial polyps was 36.24%. They were found at fundal dome areas frequently.

In analysis of endometrial polyp size with membranous adhesion, the bigger the polyp size was (Fig. 1), the larger the extent of membranous adhesion was ($p < 0.05$). However,

there was no statistically association between membranous adhesions with location, number and morphology of endometrial polyps (Table 3).

3. Hysteroscopic Finding

Membranous filmy adhesions frequently found during hysteroscopy in patients who have endometrial polyps. (Fig. 2A) After removing of endometrial polyps and membranous adhesions, relatively clear endometrial cavity was found (Fig. 2B).

4. Pathologic Finding

Membranous adhesions and membranous adhesions were found in same patients. Through Masson's trichrom staining, membranous adhesions could be found more distinct.

5. Pregnancy after Hysteroscopy

Total follow up durations were from 3 months to 4 years. So it was hard to confirm pregnancy for patients who had hysteroscopy lately. Total 13 patients were confirmed to be pregnant. Of them, 5 patients by 1st IVF cycle, 7 patients by 2nd IVF cycle and one was pregnant by natural.

DISCUSSION

Successful implantation largely depends on the embryo's quality and on uterine receptivity. The process involves complex interactions between the hormonally primed uterus and the mature blastocyst (Norwitz et al., 2001).

Structural uterine abnormalities such as leiomyomas, Müllerian anomalies, intrauterine adhesions and endometrial polyps may contribute to subfertility, implantation failure or miscarriage. Endometrial polyps are the commonest structural uterine pathology, being reported 15% to 24% of infertile women (Valle, 1980; Shokeir et al., 2004).

Endometrial polyps are commonly seen in subfertile women. They are not a significant health risk. But in infertility examination, they cannot be overlooked. Hysteroscopic polypectomy in infertile women is likely to increase pregnancy

Table 2. Features of endometrial polyps and membranous adhesions

No. of subjects	Location*	Size	Number	Type	Membranous adhesions(%)	Pregnancy**
1	LM	1.5	1	pedunculated	45	1st IVF
2	AU	0.8	1	pedunculated	20	f/u*** loss
3	AL	1.9	1	pedunculated	30	N
4	AM	1	1	pedunculated	20	N
5	LU	0.6	1	pedunculated	10	2nd IVF
6	LM	1.45	1	sessile	35	f/u loss
7	PL	1.4	1	pedunculated	60	1st IVF
8	AL	2	1	sessile	80	2nd IVF
9	LM	3	1	pedunculated	65	N
10	PM	1.5	1	pedunculated	15	1st IVF
11	PM	1.13	1	pedunculated	45	f/u loss
12	PM	0.2	1	sessile	20	2nd IVF
13	AM, AL	2.5	2	sessile	20	N
14	MU, LU	1.5	2	pedunculated	15	N
15	PL	1.2	2	pedunculated	60	N
16	AL	1.3	2	pedunculated	20	N
17	AL	1	2	pedunculated	20	f/u loss
18	PL	1.14	2	sessile	20	1st IVF
19	LU, AU	1.2	2	sessile	30	N
20	PM, LM	0.7	2	pedunculated	20	2nd IVF
21	LM, PM	0.8	2	pedunculated	55	N
22	LM, AM	1.3	2	pedunculated	40	2nd IVF
23	AL	0.5	2	sessile	20	f/u loss
24	AL, AM	1.6	multiple	pedunculated	40	f/u loss
25	AM	0.5	multiple	pedunculated	20	N
26	AU, LM	1.1	multiple	sessile	25	1st IVF
27	LU, AU	1.2	multiple	sessile	25	N
28	PL	1.25	multiple	pedunculated	40	N
29	PL	1.33	multiple	pedunculated	80	N
30	AL	1.8	multiple	pedunculated	35	2nd IVF
31	PL	1.8	multiple	sessile	55	f/u loss
32	AL	1.03	multiple	sessile	45	2nd IVF N
33	PM, PL	1.57	multiple	pedunculated	30	N
34	PM, PL	1	multiple	pedunculated	60	n-preg

*AB: A-anterior, posterior, lateral, B-upper, middle. Lower, **N: not yet confirmed, n-preg : natural pregnancy, ***f/u: follow up

rates by a factor of three to four times and the accumulate rate of pregnancies was 65.2% (Shokeir et al., 2004). Perez-

Medina et al. reported that hysteroscopic polypectomy before intrauterine insemination is an effective procedure (Varasteh

Table 3. Feature of endometrial polyps and association with membranous adhesions

Variables	No. of cases (%)	<i>p</i> -value
Number		NS
1	12(35)	
2	10(30)	
Multiple	12(35)	
Type		NS
Sessile	11(32)	
Pedunculated	23(68)	
Location		NS
Anterior	17(41)	
Posterior	14(34)	
Lateral	10(24)	
Upper	10(29)	
Middle	11(32)	
Lower	12(35)	
Variables	Mean±SD	<i>p</i> -value
Size	1.6±0.6	<0.05

NS: not significant.

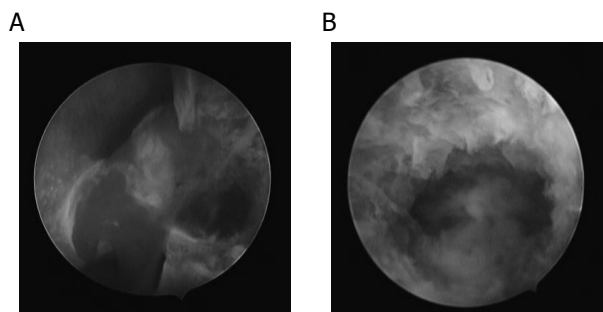


Fig. 2. Hysteroscopic finding of endometrial polyps and membranous adhesions. A: Multiple endometrial polyps with membranous adhesions, B: After removing of endometrial polyps and membranous adhesions.

et al., 1999). Thus, the existence of endometrial polyps may sometimes be a significant finding for infertility patients.

Filmy membranous adhesions in uterine cavity were thought to be preventing implantation according to previous study (Shin, 2010). They could be easily detected after methylene blue instillation during hysteroscopy. Although the mechanism how these filmy membranous adhesions

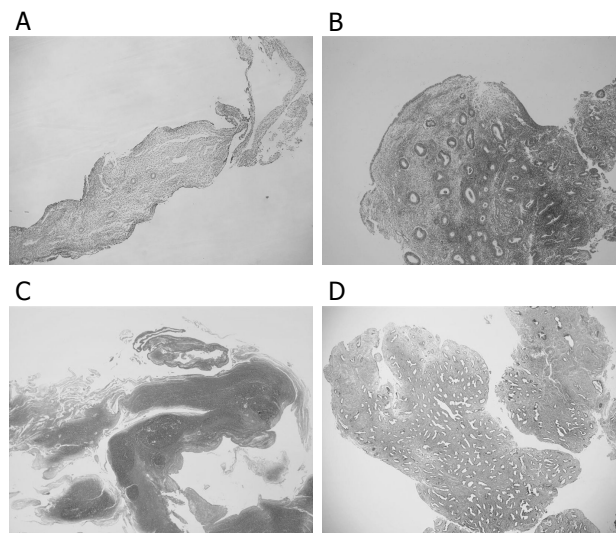


Fig. 3. Pathologic findings of endometrial polyps with membranous adhesions. A: Membranous adhesion band. (H&E staining, ×40), B: Endometrial polyp. Same patients with A. (H&E staining, ×100), C: Membranous adhesion band. (Masson's trichrom staining, ×40), D: B. Endometrial polyp. Same patients with C. (H&E staining, ×100)

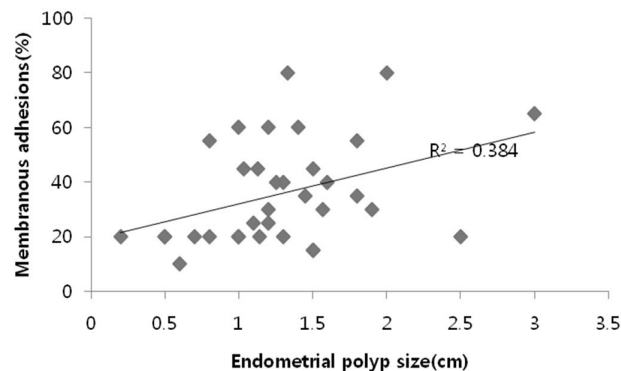


Fig. 4. Association of endometrial polyps' size with extents of membranous adhesions.

affect the implantation and the nature could not be confirmed, removal of these lesions improved pregnancy rate.

Shokeir et al. have reported endometrial polyps' location (Shokeir et al., 2004). They found that most endometrial polyps were located in the region of the uterotubal junction. Other study showed that endometrial polyps were more often at posterior uterine wall (31.7%). They also concluded that the location of the endometrial polyps may influence

pregnancy rate and fertility outcome. The pregnancy rate after surgery was 57.4% for endometrial polyps located at the uterotubal junction, 40.3% for multiple polyps, 28.5% for posterior uterine wall polyps, 18.8% for lateral uterine wall polyps and 14.8% for anterior uterine wall polyps (Yanaiharu et al., 2008). These reports were different from ours which endometrial polyps were found evenly in the uterine cavity. In addition, there was no significant association between location of endometrial polyps and membranous adhesions in our study.

To the best of our knowledge, the literature contains no reports that describe the relationship between morphologic type of endometrial polyps and pregnancy outcome. In our study, morphology of endometrial polyps was not related to membranous adhesion.

Lass et al. reported that small endometrial polyps (<2 cm) do not decrease the pregnancy rate; however, an increased pregnancy loss has been noted (Lass et al., 1999). Furthermore, endometrial polyps of size <1.5 cm do not affect intracytoplasmic sperm injection outcome (Isikoglu et al., 2006). Restoration of reproductive ability was found to be unrelated to the size of the removed lesion (Bradley et al., 2000; Lieng et al., 2007). However, a statistically significant difference, in pregnancy rate was found between women who underwent hysteroscopy before an IVF-embryo transfer cycle and those who did not undergo a hysteroscopy (Fernandez-Parra et al., 2006). Other authors report that diagnostic hysteroscopy should be used routinely in the workup of infertile woman, even in the presence of eumenorrhea (Shoekir et al., 2004). And spontaneous pregnancy and delivery at term rates were increased after polypectomy and were 67.6% and 58.8% for the patients having small polyps, while the percentages were 57.1% and 51% for patients with bigger or multiple polyps respectively (Yanaiharu et al., 2008). In our study, mean size of the endometrial polyps was 1.6 ± 0.6 cm which the largest one was 3.0 cm. And the extents of the membranous adhesions tended to be wide as the endometrial polyps were larger. It means that the size of endometrial

polyps is in direct proportion to the extent of the membranous adhesions. From of that, it can be inferred that the implantation failure was related to the size of endometrial polyps.

The mechanism by which endometrial polyps may interfere with implantation is not clear. It is biologically plausible that endometrial polyps can cause infertility due to mechanical interference with sperm and embryo transport, impairment of embryo implantation, or altered endometrial receptivity.

We hypothesize that endometrial polyps, especially the larger one, may preferentially interfere with oocyte/embryo transport. Moreover, they may act as barriers to normal menstrual flow, thus it causes menstrual regurgitation or sometimes menstrual stagnation. This hypothesis can explain why endometriosis is associated with a high risk of endometrial polyps (Licong et al., 2011). In these circumstances with stagnated menstrual flow, membranous adhesions are frequently formed.

Endometrial polypectomy has been recommended to women in whom endometrial polyps were the only obvious cause for their subfertility. But the management of endometrial polyps diagnosed at the time of ovarian stimulation for IVF remains controversial. In a retrospective case-control study, Lass et al. (1999) compared implantation and clinical pregnancy rates in women undergoing fresh embryo transfer without removing the endometrial polyps with those who had the endometrial polyps removed followed by frozen embryo transfer. Although there was a trend toward higher implantation, clinical pregnancy and live birth rates after endometrial polypectomy the difference was not statistically significant. Of note, histological diagnosis of endometrial polyp was confirmed in only 58.3% of cases.

Stronger evidence for the favorable effects of endometrial polypectomy on pregnancy outcome can be drawn from other study which included a group of women who underwent hysteroscopic endometrial polypectomy or hysteroscopy and polyp biopsy followed by IUI. In this study,

the cumulative pregnancy and live birth rates after four cycles of IUI were significantly higher in women who underwent hysteroscopic endometrial polypectomy compared with hysteroscopy and biopsy of the polyp. Furthermore Makrakis et al., reported that women with implantation failures after IVF had a remarkably high possibility for unsuspected abnormalities seen at hysteroscopy. So, they insisted that hysteroscopy could serve as a positive prognostic factor for achieving a subsequent pregnancy (Makrakis et al., 2004).

Hysteroscopy is the most effective way to remove endometrial polyps under direct vision, because blind dilation and curettage may frequently leave residual tissue or miss the whole polyp. Hysteroscopic scissors or resectoscopy is usually need to transect the endometrial polyps from the endometrium. Also, the prevalence of malignancy and atypical hyperplasia even if low should not be forgotten indicating that endometrial polyps should be removed (Lieng et al., 2007) and hysteroscopy may be a very useful tool for a precise diagnosis and treatment (Fernandez-Parra et al., 2006).

Because this study is a retrospective study with no random design, further prospective studies are required to make a comparison between women attempting pregnancy after polypectomy and those attempting pregnancy without removal of the endometrial polyps, so that the true extent of the therapeutic effect of endometrial polypectomy can be more powerfully deciphered. Although tremendous potential bias could have been introduced into the study that affected the outcome, it appears that size of endometrial polyps may be one of the reasons for infertility.

As a conclusion, in patients with repetitive failed IVF or ICSI attempts, simple diagnostic or operative hysteroscopy before a subsequent IVF or ICSI treatment is reasonable and recommended, as this intervention may improve fertility. With hysteroscopy, it is possible to examine detailed evaluation of the uterine cavity as well as decrease the occurrence of membranous adhesions through polypectomy.

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