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Histopathological profile of women who had previously failed *in-vitro* fertilization and the association to the outcome in the subsequent *in-vitro* fertilization cycle

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Objective
To evaluate the endometrial histopathological profile of patients undergoing curettage and the association of the histopathological profile with the pregnancy outcome during the subsequent *in-vitro* fertilization (IVF) cycle.

Methods
In this retrospective cohort study, a total of 248 women with at least one failed attempt of IVF and who underwent curettage and a subsequent IVF were included. Demographic data, endometrial histopathological records, stimulation information, and pregnancy outcomes were collected and analyzed.

Results
The histopathological analysis of endometrial tissues showed that 130 women (52.4%) had endometrial pathologies. Of these women, 103 (41.5%) had endometrial polyps, 22 (8.9%) had chronic endometritis, and five (2.0%) had both polyps and endometritis. No statistical difference was observed between the normal histopathology group and the abnormal histopathology group in the outcome of the subsequent IVF cycle. Subgroup analyses were performed to further characterize and compare women with normal histopathology and women with endometrial polyps (polyp subgroup) or chronic endometritis (endometritis subgroup). No statistical differences were found among the three groups in the rates of pregnancy (44.1% vs. 49.5% vs. 45.5%, *P*=0.72), biochemical pregnancy loss (13.5% vs. 15.7% vs. 20.0%, *P*=0.86), clinical pregnancy loss (25.0% vs. 31.4% vs. 30.0%, *P*=0.77), and live birth (27.1% vs. 26.2% vs. 22.7%, *P*=0.91) during the subsequent IVF cycle.

Conclusion
Women with previously failed IVF and abnormal endometrial histopathology treated with curettage had the same outcome in the subsequent IVF cycle as women with normal endometrial histopathology.

Keywords: Pathology; Polyps; Endometrium; Fertilization *in vitro*

Introduction

Implantation is the process of attachment and invasion of the blastocyst into the endometrium. Successful implantation requires the development of a receptive endometrium that is able to respond to signals from the blastocyst. This process is based on a "dialogue" between the embryo and the endometrium that is mediated by hormones, soluble growth factors, adhesion molecules, the extracellular matrix, and prostaglandins [1]. It is known that congenital anomalies

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and acquired diseases of the uterus can affect endometrial receptivity, resulting in implantation failure that manifests as recurrent pregnancy loss or infertility [2]. Therefore, uterine pathologies are considered to play an important role in the outcomes of pregnancy obtained with *in-vitro* fertilization (IVF). It is assumed that abnormal endometrial histopathology could interfere with factors that regulate the blastocyst-endometrium interplay. Many hypotheses have been published about how abnormal endometrial histopathology is likely to disturb the implantation of the human embryo [3]; however, the exact mechanism remains unclear.

Endometrial polyps can be associated with high or unopposed estrogen levels [4,5] due to factors such as anovulation, chronic tamoxifen use, and obesity. Uterine polyps have been demonstrated to be a cause of infertility in the sole prospective study in the literature [6]. Uterine polyps may be removed, which improves the outcome as opposed to not removing them [6]. However, little is understood about the outcomes in women who had uterine polyps removed as opposed to women who primarily did not have polyps. Hyperestrogenic states have been associated with altered outcomes in IVF when comparing fresh stimulations with high versus low estrogen levels [7-11]. The chronic hyperestrogenic states associated with polyps may alter outcomes even after polyp removal.

We performed this study to characterize the histopathological profile of women with previously failed IVF and who underwent endometrial curettage, to evaluate the association between the histopathological profile and the outcome in the subsequent IVF cycle.

Materials and methods

1. Patients and data collection

This retrospective cohort study included 248 women with previously failed IVF and who underwent endometrial curettage and subsequent embryo transfer between January 2015 and March 2016 at a university-affiliated reproductive center. Curettage was performed 2 weeks before initiating the subsequent IVF cycle in more than 90% of the cases. All biopsies were performed by the same physician. The histopathological analysis of endometrial tissue samples was performed by one of two pathologists at the associated university hospital.

The indications for curettage included a persistently thick baseline endometrium (greater than 5 mm) on cycle day 2 or 3 of spontaneous menses, which did not decrease to less than 5 mm on daily ultrasonography until cycle day 5, or at least two failed transfers of a high-quality blastocyst. Failed IVF was defined as at least one cycle of IVF in which at least one good-quality blastocyst was transferred without achieving a clinical pregnancy. A good-quality embryo was defined as a Gardner's grade AA, AB, or BA embryo [12].

The exclusion criteria were biopsy results suggesting malignancy or hyperplasia and the detection of intramural or submucosal fibroids or structural uterine anomalies. None of the women had recurrent pregnancy loss. None of the patients in the study had uncorrected prolactin, thyroid abnormalities, or chronic hypertension. Preimplantation genetic screening results were not available for any of the women whose data were included in this study.

Women with a diagnosis of chronic endometritis on histopathological analysis did not undergo antibiotic treatment before care. This was because, in most cases, the pathology results only became available after the start of the embryo transfer cycle and the treatment can require 14 to 21 days of antibiotics, ideally with a test of cure. This 14- to 21-day period was unavailable before transfer once the diagnosis was made in most cases. The McGill University Committee for the Protection of Human Research Subjects approved the data collection (study No. 4145).

2. Endometrial curettage

Endometrial curettage was performed under ultrasound guidance using a commercially available curette (with a bent tip at an approximately 30-degree angle and an arch 4 cm in diameter) and a manually controlled suction device attached to a syringe. The pipette was introduced into the uterine cavity through the cervix, advanced gently, and moved circularly while rotating the catheter until the entire endometrial cavity was disrupted and cleaned, as judged by the physician under ultrasound guidance. The endometrial tissue samples obtained from all women were sent for histopathological analysis.

Although, in many institutions, hysteroscopy may be the preferred method for evaluating pathology in the uterine cavity, delays in surgical hysteroscopy, which could be up to 1 year owing to the nature of the national health service system, lead to the use of curettage, which has minimal delay. In all cases, the procedure was performed within 2

months of starting the subsequent IVF cycle. Curettage was performed after the end of menstruation at any time during the rest of the follicular or luteal phase. If performed in the luteal phase, a pregnancy test was used to confirm that none of the women were pregnant. None of the pathology specimens showed decidualization or villi that could lead to suspicion of a disrupted pregnancy.

3. Histopathological analysis

The histopathological records of endometrial tissues from all included women were collected, and the results were reviewed for all patients. Endometrial tissues with a diagnosis of endometrial polyps on histopathological analysis showed hyperplastic overgrowths of the endometrial glands and stroma around a vascular core (blood vessel) that formed a sessile or pedunculated projection from the surface of the endometrium [13]. Chronic endometritis was diagnosed on the basis of histopathological characteristics such as high vascular density with endothelial swelling and proliferation, hyaline thickening of the vessel wall with luminal occlusion, fibrinoid degeneration of the vessel wall, and small-vessel thrombosis. Furthermore, concentrated build-up of plasma cells in the stroma and granular leukocytes around epithelial and blood vessels were also considered features of endometritis [14,15].

4. IVF procedure

All women included in this study had previously undergone IVF but failed to conceive. The details of the IVF cycles and luteal support have been described previously [16]. Before the initiation of the first IVF cycle, the patients underwent an evaluation of the uterine cavity on days 2 to 5 of a spontaneous or progesterone-induced menstrual cycle, using ultrasonography, hysterosalpingography, or saline ultrasonography. None of the patients were previously identified to have uterine pathologies. Another IVF cycle was initiated following the cycle at which curettage was performed. All women underwent transfer of a high-quality blastocyst, as previously described.

5. Outcome measures

The main outcomes of this study were the pregnancy and live birth rates according to the identified histopathology. Pregnancy was defined as a positive beta-hCG test. The pregnancy rate was the ratio of the number of pregnancies to the number of total cycles of embryo transfer. Biochemical pregnancy loss was defined as a failure of pregnancy to progress to the point of ultrasound confirmation after a positive beta-hCG test. Clinical miscarriage was defined as the loss of pregnancy after clinical recognition on ultrasound and before 20 weeks of gestation. The live birth rate was the ratio of the number of live births to the number of total transfers.

6. Statistical analysis

Statistical analyses were performed using SAS/STAT® software (SAS University Edition, version 9.4M5; SAS Institute Inc., Cary, NC, USA). Data were tested for normality using the Kolmogorov-Smirnov test and transformed to natural logarithms or ranks, as appropriate, when not normally distributed. Initial analysis was performed on two groups (normal histopathology group and abnormal histopathology group) for basal and pregnancy outcome endpoints. Comparisons were performed using Student's *t*-test, and proportions were compared using the chi-square test. The comparisons were performed for various reproductive parameters, IVF outcomes, and pregnancy outcomes. In the second analysis, comparisons were performed among the normal histopathology group, polyp subgroup, and endometritis subgroup. One-way analysis of variance was performed using the SAS mixed procedure to identify a main effect of the subgroup. The least-significant difference test was used to determine significant differences among subgroups. The endpoints with proportions in the subgroup analyses were compared using the chi-square test. A value of $P \leq 0.05$ indicated *a* significant difference. Data are presented as mean±standard error of the mean values or as percentages.

Results

A total of 248 women underwent curettage at the academic IVF center and met the inclusion criteria. The age of the women ranged from 23 to 46 years. The histopathological records of the endometrial tissues obtained during the procedure showed that of the 248 women, 130 (52.4%) had the following endometrial pathologies: endometrial polyps (n=103, 41.5%), chronic endometritis (n=22, 8.9%), or both endometrial polyps and chronic endometritis (n=5, 2.01%). The remaining 118 women (47.6%) did not show any ab-

normality on histopathology and were considered the normal histopathology group for comparison.

Initial statistical analysis was performed to compare the group of women with normal histopathology and the group

Table 1. Patient characteristics, demographics, diagnoses, and indications for IVF and IVF cycle characteristics in women with abnormal histopathology compared with women with normal histopathology

	Normal histopathology group	Abnormal histopathology group	*P*-value
Patient characteristic			
No. of women	118	130	-
Age (years)	35.38±0.40	35.97±0.36	0.28
No. of previous pregnancies	1.01±0.12	0.88±0.10	0.48
No. of previous term deliveries	0.30±0.05	0.31±0.05	0.91
No. of previous miscarriages	0.72±0.11	0.55±0.09	0.19
Duration of infertility (years)	3.68±0.21	4.66±0.32	0.08
Basal serum FSH (IU/L)	8.90±1.02	9.51±1.32	0.24
Basal serum estradiol (pmol/L)	165.82±7.74	205.61±18.35	0.10
Antral follicle count	16.45±1.48	15.54±1.13	1.00
Infertility diagnosis			
Diminished ovarian reserve	25 (21.2)	27 (20.8)	0.93
Endometriosis	4 (3.4)	6 (4.6)	0.62
Male factor	37 (31.4)	46 (35.4)	0.50
Polycystic ovary syndrome failed at least 6 IUI cycles	9 (7.6)	7 (5.4)	0.47
Tubal factor	4 (3.4)	7 (5.4)	0.45
Multiple factors	18 (15.2)	18 (13.8)	0.75
Same sex couples who failed at least 9 IUI cycles	3 (2.5)	2 (1.5)	0.67
Unexplained etiology	18 (15.2)	17 (13.1)	0.62
Cycle characteristics			
Maximum Endometrial thickness (mm)	9.48±0.16	9.49±0.19	0.98
No. of mature oocytes retrieved	11.63±0.68	10.08±0.61	0.07
No. of 2 pronuclear embryos	8.81±0.58	7.61±0.46	0.10
No. of day 3 embryos	8.54±0.58	6.84±0.43	<0.05
No. of blastocysts	3.76±0.30	2.90±0.25	0.02
No. of embryos transferred	1.35±0.05	1.32±0.05	0.43

Values are presented as mean±standard error of the mean values or number (%).
IVF, *in-vitro* fertilization; FSH, follicle stimulating hormone; IUI, intra-uterine insemination.

Table 2. Outcomes of IVF cycles in women with abnormal histopathology compared with women with normal histopathology

Patient characteristic	Normal histopathology group	Abnormal histopathology group	*P*-value
No. of women	118	130	-
Pregnancy rate	52/118 (44.1%)	65/130 (50.0%)	0.35
Biochemical pregnancy loss	7/52 (13.5%)	11/65 (16.9%)	0.61
Clinical pregnancy loss	13/52 (25.0%)	19/65 (29.2%)	0.61
Live birth rate	32/118 (27.1%)	35/130 (26.9%)	0.97

IVF, *in-vitro* fertilization.

of women with abnormal histopathology (Tables 1, 2). Subsequent subgroup analyses were performed to further characterize and compare women with normal histopathology and women with endometrial polyps (polyp subgroup) or chronic endometritis (endometritis subgroup) (Tables 3, 4). The five women with both polyps and chronic endometritis were excluded from the subgroup analyses.

The patients' characteristics, demographics, diagnoses, and indications for IVF and the IVF cycle characteristics are shown in Table 1. No statistical differences were found between the two groups in age, number of previous pregnancies, number of previous term deliveries, number of previous miscarriages, duration of infertility, basal serum follicle stimulating hormone (FSH) levels, basal antral follicle count, maximum serum estradiol levels, and maximum endometrial thickness at embryo transfer. No statistical differences were observed between the two groups in the diagnoses and the indications for IVF. In the comparison of IVF cycle characteristics, the number of mature oocytes and the number of zygotes with two pronuclei were similar between the normal and abnormal histopathology groups (Table 1). Nevertheless, the number of day 3 embryos and the number of blastocysts were lower in the abnormal histopathology group than in the normal histopathology group (P<0.05 and P=0.02, respectively).

Table 3. Patient characteristics, demographics, and IVF cycle characteristics in women with normal histopathology and subgroups of women with endometrial polyps (polyp subgroup) and chronic endometritis (endometritis subgroup)

Patient characteristic	Normal histopathology group	Polyp subgroup	Untreated Endometritis subgroup	*P*-value
No. of women	118	103	22	-
Age (yr)	35.38±0.40	35.91±0.40	36.14±0.93	0.52
No. of previous pregnancies	1.01±0.12	0.79±0.11	1.41±0.29	0.03
No. of previous term deliveries	0.30±0.05	0.28±0.06	0.45±0.11	0.15
No of previous miscarriages	0.72±0.11	0.48±0.10	0.91±0.27	0.07
Duration of infertility (yr)	3.68±0.21	4.72±0.37	4.60±0.66	0.20
Basal serum FSH (IU/L)	8.90±1.02	8.65±1.13	13.42±5.62	0.20
Basal serum estradiol (pmol/L)	165.82±7.74	207.64±20.21	201.54±52.61	0.28
Antral follicle count	16.45±1.48	16.66±1.27	9.55±1.36	<0.05
Maximum endometrial thickness (mm)	9.48±0.16	9.66±0.20	8.91±0.62	0.28
No. of mature oocytes retrieved	11.63±0.68	10.78±0.70	6.36±0.89	0.01
No. of 2 pronuclear embryos	8.81±0.58	8.12±0.53	5.45±0.81	<0.05
No. of day 3 embryos	8.54±0.58	7.45±0.50	4.63±0.75	0.01
No. of blastocysts	3.76±0.30	3.22±0.28	1.67±0.50	0.01
No. of embryos transferred	1.35±0.05	1.28±0.05	1.41±0.13	0.44

Values are presented as mean±standard error of the mean values or number (%).
IVF, *in-vitro* fertilization; FSH, follicle stimulating hormone.

Table 4. Pregnancy outcomes in women with normal histopathology and subgroups of women with endometrial polyps (polyp subgroup) and chronic endometritis (endometritis subgroup)

Patient characteristic	Normal histopathology group	Polyp subgroup	Untreated Endometritis subgroup	*P*-value
No. of women	118	103	22	-
Pregnancy rate	52/118 (44.1%)	51/103 (49.5%)	10/22 (45.5%)	0.72
Biochemical pregnancy loss	7/52 (13.5%)	8/51 (15.7%)	2/10 (20.0%)	0.86
Clinical pregnancy loss	13/52 (25.0%)	16/51 (31.4%)	3/10 (30.0%)	0.77
Live birth rate	32/118 (27.1%)	27/103 (26.2%)	5/22 (22.7%)	0.91

There was no significant difference in the number of transferred embryos between the two groups.

Table 2 shows the cycle outcomes (pregnancy, biochemical pregnancy loss, clinical pregnancy loss, and live birth rates) in the normal histopathology group and the abnormal histopathology group. No statistical differences were found between the two groups in the rates of pregnancy, biochemical pregnancy loss, clinical pregnancy loss, and live birth.

Table 3 shows the patient characteristics, demographics, diagnoses, and indications for IVF, and the IVF cycle characteristics in the subgroup analyses. No statistical differences were found among the three groups (normal group, polyp subgroup, and untreated endometritis subgroup) in age, number of previous term deliveries, number of previous miscarriages, duration of infertility, basal serum FSH levels, maximal serum estradiol levels, and endometrial thickness at embryo transfer (Table 3).

Significant statistical differences were found among the three groups in the number of previous pregnancies (1.01±0.12 vs. 0.79±0.11 vs. 1.41±0.29, P=0.03) and the antral follicle count (16.45±1.48 vs. 16.66±1.27 vs. 9.55±1.36, P<0.05). The difference in the numbers of previous pregnancies was due to higher (P<0.05) mean values in the endometritis subgroup than in the polyp subgroup. Meanwhile, the values in the normal histopathology group were not different from those in the other two subgroups. The difference in the antral follicle count was due to a lower (P<0.05) mean number of antral follicles in the endometritis subgroup (9.55±1.36) than in both the normal histopathology group (16.45±1.48) and the polyp subgroup (16.66±1.27).

In the comparison of IVF characteristics, statistically significant differences were found in the number of mature oocytes retrieved (11.63±0.68 vs. 10.78±0.70 vs. 6.36±0.89, P=0.01), number of zygotes with two pronuclei (8.81±0.58 vs. 8.12±0.53 vs. 5.45±0.81, P<0.05), number of day 3 embryos (8.54±0.58 vs. 7.45±0.50 vs. 4.63±0.75, P=0.01), and number of blastocysts (3.76±0.30 vs. 3.22±0.28 vs. 1.67±0.50, P=0.01). The effect for each endpoint was due to the lower (P<0.05) percentage values in the endometritis subgroup than in both the normal histopathology group and the polyp subgroup (Table 3). There was no difference in the number of transferred embryos among the three groups.

No statistical differences were found among the three groups in the rates of pregnancy, biochemical pregnancy loss, clinical pregnancy loss, and live birth (Table 4).

Discussion

It is known that inadequate uterine receptivity is responsible for some cases of implantation failures, whereas the embryo itself is also responsible for some cases. In this study, our main finding was that women with previously failed IVF (with transfer of a high-quality blastocyst) and who had abnormal endometrial histopathology had similar outcomes as women with normal histopathology once an endometrial curettage had been performed.

A previous study has demonstrated that 40% of infertile women have abnormal endometrial findings on hysteroscopy (including endometrial polyps, endometrial hyperplasia, endometritis, and adhesions) [17]. In our study, histopathological evaluation of the endometrial tissues obtained during curettage in women undergoing IVF demonstrated that 52.7% of the women had abnormal endometrial findings. It should be noted that hysterosalpingography is not a routine procedure in our territory owing to a lack of resources. Therefore, inadequate initial endometrial evaluations may have occurred. Accordingly, the rate of pathologies in our study may have been increased after IVF, as opposed to other centers where resection would have been performed before the initial care. Another reason for the higher rate of polyps seen in this study than in some other studies is most likely the population differences when comparing Europeans and North Americans. Particularly, the rates of obesity, which contributes to higher serum estrogen levels that likely stimulate uterine polyp formation, are often higher in North Americans than in other populations. However, the most likely cause of the increased rates of polyps was that the indications for curettage included a persistently thick baseline endometrium on cycle day 2 or 3 of menstruation that did not decrease to less than 5 mm on daily ultrasonography until cycle day 5. The incidence of endometrial polyps depends on the population under study and the applied diagnostic test, and endometrial polyps can be found in 1% to 41% of the subfertile population [18].

Persistent exposure to estrogen may stimulate the occurrence of irregular growths in the endometrial glands [19-21]. Advanced age, hypertension, obesity, and tamoxifen use seem to be risk factors for endometrial polyps [5]. Both obesity and treatment with tamoxifen (a selective estrogen receptor modulator with agonistic effects on the endometrium) result in a hyperestrogenic state. Hypertension is usually as-

sociated with insulin resistance, which lowers sex hormone-binding globulin levels, resulting in higher levels of bioactive estrogens [22]. Although the exact cause of polyp development is unknown, some hypotheses have been published, including monoclonal endometrial hyperplasia [23]; genetic factors that may alter the proliferative process, resulting in endometrial overgrowth and polyp formation [24]; overexpression of endometrial aromatase [25,26]; alterations in the endometrial levels of matrix metalloproteinases and cytokines [27]; and increased levels of the proliferation-regulating protein p63 [28]. The obvious question is whether the milieu that causes endometrial polyps adversely affects fertility or whether decreased fertility is caused by the polyp alone. The mechanism by which polyps may be associated with implantation failure and infertility is poorly understood [2]. Nevertheless, if polyps do play a role, it could be through the mechanism that causes polyps to occur, mainly the hyperestrogenic state that alters endometrial receptivity [29,30]. In a prospective study, Richlin et al. [31] obtained uterine flushing samples from infertile patients during the proliferative phase and found that the uterine glycodelin levels are elevated in patients with polyps when compared with controls. Glycodelin is a glycoprotein that has been shown to inhibit sperm-oocyte binding and NK cell activity. Elevated glycodelin levels in the late follicular phase could adversely affect fertilization and implantation [31].

Previous studies have shown that hysteroscopic polypectomy of endometrial polyps seemed to improve fertility and to increase the pregnancy rates in infertile women [32,33]. Nevertheless, our data suggest that women with resected polyps do not seem to have worse outcomes than those without polyps. It should be noted we cannot determine the sizes of the resected polyps because they were not visualized before resection. Whether the vast majority of patients had small polyps and whether the outcomes might have been different in a population with longer uterine polyps cannot be determined with the current data.

The question arises of whether all polyps were adequately removed using the mentioned procedure. In a series of 50 women who underwent a similar curettage before second-look office hysteroscopy (unpublished), we were able to demonstrate that in 84 percent, the endometrium was completely cleaned using this procedure, with all surfaces affected by the curettage. In the remaining eight patients, less than 20% of the wall was unaffected. During this series, it was noted that in all women with endometrial polyps at first-look hysteroscopy, the polyps were removed in 100% of the cases and no further treatment was required. It should also be noted that had polyps remained present after attempting resection, we could have expected the outcomes to be worse in that group, which did not occur [6]. It may also be questioned why a curettage was performed in these cases rather than other procedures. Socialized medicine introduces waiting times for many procedures in our local area. As the waiting time for hysteroscopy can reach up to 12 months for benign conditions, curettage is preferred in our region if it can adequately treat the pathology.

Chronic endometritis is a condition characterized by the presence of plasma cells in the endometrial stroma. Most cases are asymptomatic or accompanied by mild disturbances and cannot be detected with ultrasound and hysterosalpingography [34]. Chronic endometritis can adversely affect infertility and endometrium receptivity. The bacteria in the endometrium lead to abnormal lymphocyte counts and, consequently, to an environment that interrupts normal endometrial receptivity [35]. Cicinelli et al. [34] found that chronic endometritis is common in women with RIF and antibiotic treatment significantly improves the reproductive outcome at a subsequent IVF cycle.

Another study showed that chronic endometritis was identified in 30.3% of patients with recurrent implantation failure (RIF). Patients with RIF who had chronic endometritis had lower implantation rates (11.5%) in the IVF cycle following endometrial sampling than patients who had RIF but were negative for chronic endometritis (32.7%) and patients with RIF who did not undergo endometrial sampling (controls) (20.3%) (P=0.0024). The clinical pregnancy and ongoing pregnancy rates were similar across groups [36]. Meanwhile, Kasius et al. [37] reported that the prevalence of chronic endometritis in asymptomatic infertile women with normal transvaginal ultrasonography was 2.8%. Moreover, the reproductive outcome after the initiation of IVF/intracytoplasmic sperm injection was not found to be negatively affected by chronic endometritis. The conclusion was that the clinical implication of chronic endometritis seems minimal [37]. In our study, the presence of chronic endometritis that remained untreated did not affect the outcomes.

The reasons for the lower antral follicle count, lower number of mature oocytes retrieved, lower number of two pronuclear zygotes after *in vitro* fertilization, lower number

of day 3 embryos, and lower number of blastocysts in the chronic endometritis subgroup than in the normal histopathology group and the polyp subgroup are not known. A previous study reported no differences in the number of oocytes retrieved and the fertilization rates between women with and without chronic endometritis [36]. We believe that this difference was sporadic and therefore did not affect the outcomes.

This study has several strengths. This is the first study to evaluate the histopathological profile of women with previously failed IVF and its association with the outcome in the subsequent IVF cycle. The number of patients was large, and there were no significant differences among the groups in terms of demographics and clinical characteristics. However, this study also has several weaknesses. It was a retrospective study with potential allocation bias. The number of patients with chronic endometritis was small, making the conclusion tenuous. Because specific specimen staining is not performed for chronic endometritis at our institution, the rates may have been incorrectly estimated. Nevertheless, this likely represents the clinical situation at many institutions worldwide and thus is reflective of the true treatment conditions. However, body mass index (BMI) values were not reliably recorded in many patients. High BMI may be associated with lower pregnancy outcomes and with uterine polyps, owing to the induced hyperestrogenic state. However, as the outcomes did not differ between the groups that did and did not have polyps resected, the BMI was likely similar in the two groups; otherwise, the outcomes may have been favorable in the group without polyps owing to the implied lower BMI. The number of women with poly cystic ovary syndrome (PCOS) is shown in Table 1, and these women were included in the two groups at similar proportions. This implies that both groups included women with a hyperestrogenic state. However, it is also likely that the two PCOS groups differed in that one group had abnormal pathology while the other did not, and are worthy of this comparison.

In conclusion, the current study evaluated the relationship between the endometrial histopathological profile of patients who underwent endometrial curettage and the outcome of IVF and the pregnancy characteristics during the subsequent IVF cycle. Women with previously failed IVF and abnormal endometrial histopathology caused by uterine polyps had the same IVF outcome in the subsequent IVF cycle as women with normal endometrial histopathology. This suggests that the cause of endometrial polyps did not alter the endometrial receptivity, including a hypothesized chronic hyperestrogenic state. Although the number of patients with chronic endometritis was small, untreated chronic endometritis may not have altered the IVF outcomes. However, further large studies, particularly prospective studies, on the relationship between chronic endometritis and IVF outcomes are needed.

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (ethics approval was obtained from our institution; study No. 4145) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient consent

Informed consent was not required because this was a retrospective study.

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