Histological diagnostic criterion for chronic endometritis based on the clinical outcome.

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Abstract

**Background:** Chronic endometritis is a slight inflammation of the endometrium that is histologically diagnosed mainly by the presence of plasma cells in the endometrial stroma. In many previous clinical studies, the clinical outcomes were compared between the group cured with antibiotics and the persistent group, and the subjects were patients with recurrent implantation failure. However, antibiotics cannot be administered without establishing diagnostic criteria in advance. It is also difficult to purely evaluate the effect of chronic endometritis on implantation when the control group is defined as patients with recurrent implantation failure without chronic endometritis, since the pregnancy rate in patients with recurrent implantation failure will be lower due to the presence of causes other than chronic endometritis for implantation failure. For these reasons, there appear to be no uniform criteria based on clinical outcomes that are accepted worldwide.

**Methods:** A prospective observational study was conducted in a single university from June 2014 to September 2017. Patients who underwent single frozen-thawed blastocyst transfer with a hormone replacement cycle after histological examination for the presence of chronic endometritis were enrolled. Participants with recurrent implantation failure, recurrent pregnancy loss, and diseases suspected to cause implantation failure were excluded. Four criteria were used to define chronic endometritis according to the number of plasma cells in the same group of patients: 1 or more plasma cells, 2 or more, 3 or more, or 5 or more in 10 high-power fields. Pregnancy rates, live birth rates, and miscarriage rates of the Non-chronic endometritis and the chronic endometritis groups defined with each criterion were calculated.

**Results:** The pregnancy rate and live birth rate of Non-chronic endometritis was highest and all P values for pregnancy rates, live birth rates, and miscarriage rates were smallest when the diagnostic criterion of chronic endometritis was defined as the presence of one or more plasma cells in 10 high-power fields.

**Conclusion:** Chronic endometritis should be diagnosed as the presence of one or more plasma cells in 10 high-power fields. According to this diagnostic criterion, chronic endometritis adversely affected the pregnancy rate and the live birth rate.
Background

Chronic endometritis (CE) is defined as slight inflammation of the endometrium and is generally agreed that the presence of plasma cells within the endometrial stroma is the most useful histologic criterion for diagnosis [1–6]. Although patients with CE have no or subtle clinical symptoms, and no clinical significance has yet been found, there have recently been many reports that show its relationship with infertility and implantation failure [4, 7–15].

Epidemiologically, CE is recognized in 2.8–67.6%, from a very low frequency to a very high frequency, of patients with infertility and implantation failure [4, 7, 10–15]. Bacterial infection is related to the cause of CE, because many cases of CE are cured by antibiotics [7–9, 14, 16–18]. It has been reported that the clinical outcomes of in vitro fertilized embryo transfer are improved when cure of CE is confirmed after administration of antibiotics for recurrent implantation failure (RIF) [9, 14, 16–18]. However, on the other hand, there have been reports that administration of antibiotics is ineffective, and reports that CE does not affect fertility at all [4, 7]. Although the cause of the differences in the research results regarding the effects of CE on fertility may be due to different patient backgrounds and subjects in each study, we considered that the biggest problem is the difference in the diagnostic criteria for CE in each study. In many previous clinical studies of CE, the study subjects were patients with RIF, and the clinical outcomes were compared between the group cured with antibiotics and the persistent group. However, antibiotics cannot be administered without establishing diagnostic criteria in advance. Thus, this methodology interferes with the determination of CE criteria depending on the clinical outcomes. Moreover, it is also difficult to purely evaluate the effect of CE on implantation when the control group is defined as patients with RIF without CE, since the pregnancy rate in patients with RIF will be lower in subsequent treatment cycles due to the presence of causes other than CE for implantation failure. For these reasons, there appear to be no uniform criteria based on clinical outcomes that are accepted worldwide.

In this study, participants with RIF, RPL, and diseases suspected to cause implantation failure were excluded when participants were enrolled, and 4 different diagnostic criteria for CE, based on the number of plasma cells in 10 high-power fields (HPFs) (field magnified 400x with microscope) for the
same group of participants in which tissue was collected immediately before single frozen-thawed blastocyst transfer, were evaluated. Then, the pregnancy rate and live birth rate were examined with each histologic diagnostic criterion. This is the first prospective study of criteria for CE based on clinical outcomes.

Methods

This study was approved by the Ethics Committee of Shiga University of Medical Science (registration number 2014-090). All clinical studies were conducted according to the Declaration of Helsinki for Medical Research involving Human Subjects. Informed consent was obtained from the participants. The subjects were patients under 41 years of age who agreed and underwent the in vitro fertilization-embryo transfer (IVF-ET) protocol of our department, which includes routine hysteroscopy and local endometrial curettage (injury) before first frozen thawed embryo transfer. The patients were enrolled from June 2014 to September 2017. Patients who had a history of RIF, recurrent pregnancy loss (RPL) or suffering from genetic disorders, endocrine and autoimmune diseases, submucosal myoma, adenomyosis, uterine malformation, or endometrial thinning (< 8 mm at implantation phase) were excluded. RIF was defined as the failure of clinical pregnancy after 4 good quality embryo transfers, with at least three fresh or frozen IVF cycles, as per Coughlan et al [19]. RPL was defined as the patient with 3 or more miscarriage [20].

As shown in Fig. 1, IVF or intracytoplasmic sperm injection was performed with a gonadotropin releasing hormone (GnRH) agonist protocol or a GnRH antagonist protocol, and the blastocysts were frozen. The ovulation day was then identified using a urine ovulation test and examination with ultrasonography, and hysteroscopy and endometrial tissue collection were performed 5–9 days after ovulation. Whether endometrial macropolyps and uterine malformations were present was determined by hysteroscopy, and patients with these diseases were excluded from this study at that moment. Immediately after hysteroscopy, the tissue around the center of the anterior endometrium was collected with 4.5 J. A. M. W Type Uterine Curettes, and immunostaining of this sample for CD138 was performed, as reported previously [21, 22]. One pathologist examined this tissue to determine how many plasma cells there were in 10 random HPFs (Olympus BX-41; hpf diameter = 0.55 mm; hpf
area = 0.24 mm$^2$) of the endometrial stromal area.

The first aim of the present study was to determine if the pregnancy rate and ongoing pregnancy rate were different when CE was diagnosed with one or more plasma cells found in 10 HPFs of the endometrial stromal tissue at the implantation phase, which exactly matches the histological diagnosis, compared with the patients without any plasma cells found. The next research aim was to examine whether the pregnancy rate, live birth rate, and miscarriage rate differ between Non-CE and CE when the diagnostic criteria for CE are changed. That is, four different criteria for CE were used according to the number of plasma cells: one or more plasma cells in 10 HPFs; 2 or more plasma cells in 10 HPFs; 3 or more plasma cells in 10 HPFs; and 5 or more plasma cells in 10 HPFs. Pregnancy rates, live birth rates, and miscarriage rates were calculated in the Non-CE and CE groups for each criterion.

Blastocysts were transferred within 90 days of endometrial tissue collection. An estradiol patch was started on days 2–3 of menstruation and increased gradually (Fig. 3). When the endometrial thickness reached 8 or more mm, oral administration of dydrogesterone (DYD) was started (40 mg/day for patients weighing less than 65 kg or 60 mg for those weighing 65 kg or more). Single frozen-thawed blastocyst transfer was performed 6 days after DYD administration, and a blood human chorionic gonadotropin (hCG) test was performed 2 weeks after blastocyst transfer. When hCG was detected, ultrasonography was performed within one week from that day, and those with a gestational sac in utero were defined as pregnant. When pregnancy was recognized, administration of these hormones was continued until 13 to 15 weeks of pregnancy. When the patients did not conceive or miscarriage resulted, their administration was discontinued as appropriate.

The target number of participants in the present study was calculated based on a retrospective study reported by Cicinelli et al [9]. According to their report, when CE was cured with antibiotics, the ongoing pregnancy rate was 60.8% (28/46), but when it persisted, the rate was 13.3% (2/15); there was a significant difference between them. Based on these results, the number of patients required for enrollment was calculated using software provided by the Department of Biostatistics, Vanderbilt University (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize). In the section of
Dichotomous, independent, prospective, two proportion, and Fisher’s exact test were selected to measure the sample size. An $\alpha$ of 0.05 was selected as the probability of falsely rejecting the null hypothesis, with 0.8 for power (the probability of always rejecting the null hypothesis if the null hypothesis is false in the statistical hypothesis test), 0.605 for $P0$ (the probability of the outcome for a control patient in prospective studies), and 0.133 for $P1$ (the probability of the outcome in an experimental subject in prospective studies). When a value of 1 was selected for $m$ (the ratio of control to experimental subjects for independent prospective studies), it was calculated that enrollment of 19 cases was necessary for each group. When $m$ was chosen as 0.56, 0.36, 0.26 and 0.55, the number of cases required for control (Non-CE) and CE became 26 and 15, 33 and 12, 42 and 11, and 26 and 15, respectively.

Statistical analysis was performed using Graph Pad Prism 5 (GraphPad Software Inc., La Jolla, CA). The normality of the distribution of each dataset was analyzed using the Kolmogorov-Smirnov test, and then Student’s $t$-test or the non-parametric Mann-Whitney U test was used depending on the distribution pattern. The significance of differences in pregnancy, live birth, and abortion rates between the Non-CE and CE groups was examined using Fisher’s test. A significant difference was defined as a P value less than 0.05.

Results
A total of 69 patients were registered (Figure 2). Of these, patients who wanted treatment with antibiotics, two-step embryo transfer, two-embryo transfer, or stimulated endometrium embryo transfer (SEET) were excluded, and 53 patients were finally analyzed.

When CE was defined as one or more plasma cells in 10 HPFs, there were 27 Non-CE patients and 26 CE patients. When CE was defined as 2 or more 2 plasma cells in 10 HPFs, 3 or more plasma cells in 10 HPFs, or 5 or more plasma cells in 10 HPFs, the numbers of Non-CE patients and CE patients were 34 and 19, 39 and 14, and 42 and 11, respectively. These met the statistically required numbers.

When the diagnostic criterion for CE was the presence of one or more plasma cells in 10 HPFs, there were no differences between the two groups in patients’ background except parity (Table 1). The pregnancy rate, live birth rate, and miscarriage rate were 63.0% vs 30.8% (P=0.028), 51.9% vs 7.7%
(P=0.0007), and 17.7% vs 75% (P=0.0099) in the Non-CE and CE groups, respectively. The pregnancy rate and live birth rate were significantly lower in the CE group, and the miscarriage rate was significantly higher in the CE group.

When the diagnostic criterion for CE was the presence of two or more plasma cells in 10 HPFs, there were no differences between the two groups in patients’ background except age and parity (Table 2). The pregnancy rate, live birth rate, and miscarriage rate were 58.8% vs 26.3% (P=0.043), 44.1% vs 5.3% (P=0.0041), and 25% vs 80% (P=0.04) in the Non-CE and CE groups, respectively. The pregnancy rate and live birth rate were significantly lower in the CE group, and the miscarriage rate was significantly higher in the CE group.

When the diagnostic criterion for CE was the presence of three or more plasma cells in 10 HPFs, there were no differences between the two groups in patients’ background except age, gravidity, and parity (Table 3). The pregnancy rate, live birth rate, and miscarriage rate were 53.9% vs 28.6% (P=0.13), 38.5% vs 7.1% (P=0.041), and 28.6% vs 75% (P=0.12) in the Non-CE and CE groups, respectively. The live birth rate was significantly lower in the CE group, but there were no differences in the pregnancy rate and the miscarriage rate between the groups.

When the diagnostic criterion for CE was the presence of five or more plasma cells in 10 HPFs, there were no differences between the two groups in patients’ background except age and parity (Table 4). The pregnancy rate, live birth rate, and miscarriage rate were 50% vs 36.4% (P=0.51), 35.7% vs 9.1% (P=0.14), and 28.6% vs 75% (P=0.12) in the Non-CE and CE groups, respectively. There were no significant differences in the pregnancy rate, live birth rate, and miscarriage rate.

Discussion
In the present study, diagnostic criteria for CE using endometrial specimens were prospectively evaluated based on clinical outcomes in patients undergoing a uniform program of single blastocyst transfer in hormone replacement cycles after excluding participants with RIF, RPL, and diseases suspected to cause implantation failure when participants were enrolled. The pregnancy rate and live birth rate of the Non-CE group were highest when the diagnostic criterion for CE was the presence of one or more plasma cells in 10 HPFs. The pregnancy rate and live birth rate of the Non-CE group
decreased gradually as the minimum number of plasma cells in 10 HPFs for the diagnostic criterion for CE increased from two to five. On the other hand, the miscarriage rate of the Non-CE group was the lowest when the diagnostic criterion for CE was the presence of one or more plasma cells in 10 HPFs.

When the live birth rate was compared between the patients in whom no plasma cells were found and the patients in whom one to four plasma cells were found in 10 HPFs, it was significantly lower in those with one to four plasma cells in 10 HPFs (Table 5). This result also provides evidence that the live birth rate decreases even when there are only a small number of plasma cells in 10 HPFs.

All P values for the pregnancy rate, live birth rate, and miscarriage rate were the smallest when the diagnostic criterion of CE was the presence of one or more plasma cells in 10 HPFs. Their P values increased gradually as the minimum number of plasma cells in 10 HPFs for the diagnostic criterion for CE increased from one to five. When the diagnostic criterion for CE was the presence of five or more plasma cells in 10 HPFs, there were no significant differences in the pregnancy rates and live birth rates.

In the previous reports, the subjects of clinical studies of CE have been patients with RIF treated with antibiotics to improve their clinical outcomes. However, antibiotics cannot be administered without establishing the diagnostic criteria in advance. Thus, this methodology interferes with the determination of CE criteria depending on the clinical outcomes. Moreover, it is also difficult to evaluate the pure effect of CE on implantation when the control group is defined as patients with RIF without CE, since the pregnancy rate in patients with RIF will be lower in subsequent treatment cycles due to the presence of causes other than CE for implantation failure. For these reasons, there appear to be no uniform criteria based on clinical outcomes that are accepted worldwide. The current study included patients undergoing IVF, but excluded patients with RIF, RPL, and causes of implantation failure when enrolled. For such patients, we have proven that those with even a few plasma cells in the endometrial stromal area should be diagnosed with CE because of their lower pregnancy rate and live birth rate. This result also indicates that the presence of CE adversely affects implantation, regardless of the presence of RIF, in the patients treated with IVF. The live birth rates differed more
significantly (6.25-fold, 51.9% vs. 7.7%) between the CE and Non-CE groups compared with the previous report (4.5-fold) [9], which may be due to the fact this study did not include patients with implantation failure as control group because the cause of implantation failure other than CE such as uterine anomaly may be related to miscarriage. It has been reported that the prevalence of CE is high in patients undergoing IVF. In the future, it will be necessary to examine whether the pregnancy rate and the live birth rate are improved by the diagnosis and cure of CE in patients without RIF.

DYD was used in the present study as supplementation for luteal support. As a recent report suggested, the efficacy of oral administration of DYD for luteal support in fresh embryo transfer is equivalent or superior to that of a progesterone vaginal suppository [23-25]. It has been reported that peristalsis of the endometrium in CE patients is different from that in Non-CE patients [26]. We thought that this difference in peristalsis might affect progesterone absorption into the endometrium from the vagina. Because of these reasons, it was decided to use DYD in the present study.

The numbers of the patients were relatively small. This appear to be limitations of this study. However, the number of samples required for this prospective study was calculated based on the results of a similar retrospective clinical study in the past. The difference in the ongoing pregnancy rate in that study was 4.5-fold between cured CE patients and persistent CE patients. However, in the present study, the difference between Non-CE patients and CE patients was 6.25-fold, showing that CE had more detrimental effects on implantation than expected. Considering that a greater difference exists in the live birth rate between the two groups, the number of participants in the present prospective study was considered appropriate, since statistically small numbers of participants are considered enough.

Recently, it has also been suggested that the pregnancy rate and the live birth rate were improved when CE was cured by antibiotic administration. The present study was conducted before a meta-analysis reported the effect of antibiotics for CE on the clinical outcomes of IVF [18]. When the present study was conducted, it was already beginning to be thought that antibiotics might be effective for the improvement of CE patients. Thus, it was difficult to recruit participants for the study, because the potential of antibiotics was explained to the patients. Furthermore, we began to treat CE
patients with antibiotics or another protocol using a supplement for CE patients since January 2018, after this meta-analysis was reported [18]. Given this situation, we think that it will be difficult to conduct similar prospective studies in our facilities in the future, although this situation is the same around the world.

Conclusions
The present prospective study showed that the pregnancy rate, live birth rate, and miscarriage rate of the Non-CE group differed depending on the diagnostic criteria for CE. Even when very few plasma cells are found in the endometrial stroma area of patients, the pregnancy rate and live birth rate are lower than in patients without plasma cells, and it is considered that such cases with few plasma cells in the endometrial stromal area should be diagnosed with CE. Thus, CE should be diagnosed when one or more plasma cells in 10 HPFs are found. With this diagnostic criterion, it was shown that CE adversely affected the pregnancy rate and the live birth rate in IVF, even in patients without evidence of RIF, RPL, or diseases suspected to be causes of implantation failure.

Declarations

**Ethics approval and consent to participate:** This study was approved by the Ethics Committee of Shiga University of Medical Science (registration number 2014-090). All clinical studies were conducted according to the Declaration of Helsinki for Medical Research involving Human Subjects. Informed consent was obtained from the participants.

**Consent for publication:** Consent for publication was obtained from all the participants.

**Availability of data and materials:** We can provide the raw data. The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

**Competing interests:** No author has any conflict of interest to disclose.

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**Authors’ contributions:** Conception and design: FK; acquisition of data: HK, FK, AN, JK, AM, TH, AT, AT, TA, ST, SK; analyzed the data: HK, FK, TA, ST, SK, RK; drafting the manuscript: HK, FK; substantively revised it: RK; final approval of the version: TM. All authors read and approved the final
manuscript.

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Abbreviations
CE; chronic endometritis, DYD; dydrogesterone, HPF; high-power field, IVF; in vitro fertilization, RIF; recurrent implantation failure, RPL; recurrent pregnancy loss

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Tables
Table 1. Patients' characteristics and clinical outcomes of the Non-CE and CE groups when CE was defined as one or more plasma cells in 10 HPFs

|                             | Non-CE   | CE       | P  |
|-----------------------------|----------|----------|----|
|                             | N=27     | N=26     |    |
| Age (y), Mean±SEM           | 35.0±0.63| 36.2±0.68|    |
| Gravidity, Median           | 0 (0-2)  | 0 (0-2)  | t  |
| Parity, Median, Mean        | 0 (0-1), 0.07 | 0 (0-1), 0.31 | 0  |
| FSH (mIU/mL), Median        | 8.1(4.8-24) | 9.1(5-12.5) |    |
| Previous OPU cycles, Median | 1(1-7)   | 1.5(1-6) | t  |
| EM thickness (mm), Mean±SEM | 10.3±0.31| 10.5±0.47| t  |
| Rate of good blastocysts (%)| 59.3 (16/27) | 65.4 (17/26) | t  |
| Pregnancy rate (%)          | 63.0(17/27) | 30.8 (8/26) | 0  |
| Ongoing pregnancy rate (%)  | 51.9 (14/27) | 7.7 (2/26) | 0. |
| Miscarriage rate (%)        | 17.73/17 | 756/8   | 0  |

Non-CE: non chronic endometritis, CE: chronic endometritis, HPF: high-power field, FSH: follicle stimulate hormone, OPU: ova pick up, EM thickness: endometrial thickness
Table 2. Patients’ characteristics and clinical outcomes of the Non-CE and CE groups when CE was defined as two or more plasma cells in 10 HPFs

|                                | Non-CE   | CE     | P    |
|--------------------------------|----------|--------|------|
|                                | N=34     | N=19   |      |
| Age (y), Median                 | 36(29-40)| 38(28-40)| 0.028|
| Gravidity, Median               | 0 (0-2)  | 0 (0-2)|      |
| Parity, Median, Mean            | 0 (0-1), 0.059| 0 (0-1), 0.42| 0.13 |
| FSH (mIU/mL), Median            | 8.85(4.8-24)| 8.8(5-12.5)| 0.97 |
| Previous OPU cycles, Median     | 1.5(1-7) | 1(1-5) |      |
| EM thickness (mm), Mean±SEM     | 10.5±0.35| 10.2±0.45| 0.55 |
| Rate of good blastocysts (%)    | 61.2 (21/34)| 63.1 (12/19)| 0.99 |
| Pregnancy rate (%)              | 58.8(20/34)| 26.3 (5/19)| 0    |
| Ongoing pregnancy rate (%)      | 44.1 (15/34)| 5.3 (1/19)| 0.0023|
| Miscarriage rate (%)            | 255/20   | 804/5  |      |

Non-CE: non chronic endometritis, CE: chronic endometritis, HPF: high-power field, FSH: follicle stimulate hormone, OPU: ova pick up, EM thickness: endometrial thickness

Table 3. Patients’ characteristics and clinical outcomes of the Non-CE and CE groups when CE was defined as three or more plasma cells in 10 HPFs
|                      | Non-CE        | CE            | P       |
|----------------------|---------------|---------------|---------|
|                      | N=39          | N=14          |         |
| Age (y), Median      | 36 (29-40)    | 38 (28-40)    | 0.0051  |
| Gravidity, Median    | 0 (0-2)       | 0.5 (0-2)     | 0.04    |
| Parity, Median       | 0 (0-1)       | 0.5 (0-1)     | 0.0006  |
| FSH (mIU/mL), Median | 8.85 (4.8-24) | 8.8 (5-12.5)  | 0.97    |
| Previous OPU cycles, Median | 1 (1-7) | 1.5 (1-5)     |         |
| EM thickness (mm), Mean±SEM | 10.5±0.32 | 10.0±0.54     |         |
| Rate of good blastocysts (%) | 64.1 (25/39) | 57.1 (8/14)   |         |
| Pregnancy rate (%)   | 53.9 (21/39)  | 28.6 (4/14)   |         |
| Ongoing pregnancy rate (%) | 38.5 (15/39) | 7.1 (1/14)    | 0.041   |
| Miscarriage rate (%)  | 28.66/21      | 753/4         |         |

Non-CE: non chronic endometritis, CE: chronic endometritis, HPF: high-power field, FSH: follicle stimulate hormone, OPU: ova pick up, EM thickness: endometrial thickness

Table 4. Patients’ characteristics and clinical outcomes of the Non-CE and CE groups when CE was defined as five or more plasma cells in 10 HPFs
|                                | Non-CE       | CE          | P  |
|--------------------------------|--------------|-------------|----|
| Age (y), Median                | 36 (29-40)   | 38 (28-40)  |    |
| Gravidity, Median              | 0 (0-2)      | 0 (0-2)     |    |
| Parity, Median, Mean           | 0 (0-1), 0.12| 0 (0-1), 0.45|    |
| FSH (mIU/mL), Median           | 8.7 (4.8-24) | 9 (7.4-12.5) |    |
| Previous OPU cycles, Median    | 1.5 (1-7)    | 1 (1-5)     |    |
| EM thickness (mm), Mean±SEM    | 10.4±0.31    | 10.2±0.65   |    |
| Rate of good blastocysts (%)   | 59.5 (25/42) | 72.3 (8/11) |    |
| Pregnancy rate (%)             | 50 (15/42)   | 36.4 (4/11) |    |
| Ongoing pregnancy rate (%)     | 35.7 (15/42) | 9.1 (1/11)  |    |
| Miscarriage rate (%)           | 28.66/21     | 753/4       |    |

Non-CE: non chronic endometritis, CE: chronic endometritis, HPF: high-power field, FSH: follicle stimulate hormone, OPU: ova pick up, EM thickness: endometrial thickness

Table 5. Clinical outcomes when compared between patients without plasma cells and patients with one to four plasma cells in 10 HPFs

|                                | Non-CE       | CE          |
|--------------------------------|--------------|-------------|
|                                | N=27         | N=15        |
| Pregnancy rate (%)             | 63.0 (17/27) | 33.3 (4/15) |
| Ongoing pregnancy rate (%)     | 51.9 (14/27) | 8.3 (1/15)  |
| Miscarriage rate (%)           | 17.6 (3/14)  | 66.7 (3/4)  |

Non-CE: non chronic endometritis, CE: chronic endometritis, HPF: high-power field
Protocol for the present study. Blastocysts were frozen following oocyte retrieval. Hysteroscopy and endometrial sampling were performed, and the number of plasma cells in 10 high-power fields (HPFs) of stromal area was evaluated with CD138 antibody staining of the endometrium. Single frozen-thawed blastocyst transfer was performed within 90 days after the endometrial evaluation with a hormone replacement cycle.
Patients enrolled. Sixty-nine patients were recruited, and 16 patients were excluded. Fifty-seven patients were finally analyzed.
Protocol of single frozen-thawed blastocyst transfer with a hormone replacement cycle

Multiple estradiol patches are started on days 2-3 of menstruation and increased gradually. When the endometrial thickness reaches 8 or more mm, oral administration of dydrogesterone (DYD) is started. Single blastocyst transfer is done 6 days after DYD is started.