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Effect of Natural Cycle Endometrial Preparation for Frozen-Thawed Embryo Transfer in Patients with Advanced Endometriosis

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Background: The aim of this study was to investigate the effect of natural cycle (NC) endometrial preparation for frozen-thawed embryo transfer (FET) in women with advanced endometriosis.

Material/Methods: This retrospective study included 179 patients with stage III–IV endometriosis who underwent 233 FET cycles at a tertiary care academic reproductive medical center between March 2011 and August 2013 (group A). The control group included 258 patients with tubal factor infertility who underwent 300 FET cycles (group B). Both groups were prepared for FET using a NC protocol. Rates of implantation, clinical pregnancy, live birth, ongoing pregnancy, miscarriage, and pregnancy complication were recorded.

Results: The implantation rate (A: 36.0%, B: 30.4%, P=0.06), the pregnancy rate (A: 50.2%, B: 45.3%, P=0.263), and the live birth rate (A: 39.91%, B: 39.0%, P=0.428) were similar between the stage III–IV endometriosis and tubal factor infertility groups. No differences were observed in ongoing rates of pregnancy, miscarriage, and pregnancy complications, independent of endometriosis severity. No congenital birth defects were found. When high-quality embryos are transferred, pregnancy results were not affected by active endometriosis. Although severe endometriosis did not affect birth rate, higher frequencies of premature delivery (mean gestational age A: 37 weeks, B: 38.3 weeks, P=0.044) and low birth weight were observed (<2500 g A: 26.4%, B: 16.6%, P=0.047).

Conclusions: There was no difference in pregnancy outcomes between patients with endometriosis and those with tubal infertility. Pregnancy outcomes in patients with endometriosis were not affected by endometriosis severity. Pregnancy outcomes were not affected by active endometrial cyst.

MeSH Keywords: Embryo Transfer • Endometriosis • Pregnancy Outcome

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Background

The rate of endometriosis is estimated to be approximately 10–15% in women of reproductive age and 25–50% in infertile women [1]. Several mechanisms for the association of endometriosis with infertility have been proposed, including altered pelvic anatomy, impaired ovarian function, distorted microenvironment, altered endometrial receptivity, and reduced oocyte/embryo quality [2].

Improvements in controlled ovarian hyperstimulation (COH) using gonadotropin-releasing hormone agonist (GnRH-a) may suppress some of the negative effects of endometriosis on pregnancy [3]. However, there is no consensus concerning the impact of endometriosis on the outcomes of *in vitro* fertilization (IVF)/intra-cytoplasmic sperm injection (ICSI). Patients with stage III/IV endometriosis have lower IVF/ICSI implantation rates, cumulative pregnancy rates, and lower live-birth rates compared with women with mild endometriosis or tubal factor infertility [4]. However, several studies have shown that patients with endometriosis who underwent IVF/ICSI achieved outcomes similar to those of patients with tubal infertility [3].

During IVF fresh embryo transfer cycles, the endometrium and embryo are exposed to supra-physiological concentrations of estradiol and progesterone for ovarian stimulation, which could affect endometrium receptivity and pregnancy outcomes of patients with endometriosis [5,6]. Frozen-thawed embryo transfer (FET) not only achieves higher pregnancy rates but, most importantly, also generates lower maternal and infant morbidity and mortality than fresh embryo transfer does [7]. Few studies have been conducted on endometrial preparation protocols following FET cycles in patients with advanced endometriosis. No compelling advantage for one protocol over another has been established, and the optimal protocol for FET with endometriosis is still under debate [4,8–10]. At present, endometrial preparation protocols following FET cycles in patients with endometriosis mainly include pituitary down-regulation with long-term GnRH-a administration [11]. GnRH-a downregulation for endometrial preparation can completely and effectively suppress the pituitary gland and improve the embryo quality and endometrium receptivity in women with endometriosis [12,13]. However, data regarding the effectiveness of this protocol on endometrial receptivity are controversial. Indeed, Simon et al. [6] investigated whether low levels of exogenous estrogen can hold the window of receptivity for an extended period of time since high doses of estrogen can rapidly induce a refractory state. In addition, some patients may have adverse reactions to large doses of exogenous estrogen.

There are few studies about natural cycle (NC) endometrial preparation protocols following FET cycles in patients with advanced endometriosis. NC-FET does not require the administration of exogenous hormones and, thus, maintains natural physiological conditions, which minimally affects the endometrium and is easily accepted by patients [14]. However, the pregnancy outcomes following NC-FET and the transfer of high-quality embryos are still unknown for patients with severe endometriosis, as well as the rates of pregnancy complications and birth defects.

Therefore, the aim of the present study was to analyze the influence of FET cycles on pregnancy outcomes in patients with advanced endometriosis undergoing NC endometrial preparation, and to investigate whether severe endometriosis influences pregnancy outcomes and whether FET without pituitary down-regulation with GnRH-a has benefits in patients with severe endometriosis.

Material and Methods

Patients

This was a retrospective study of the use of NC for endometrial preparation following FET cycles in patients with endometriosis at a tertiary reproductive medical center. Patients with endometriosis were diagnosed by laparoscopy or laparotomy, and all were treated surgically. Endometriosis was staged according to the revised American Society for Reproductive Medicine (ASRM) classification [15]. All patients enrolled in the present study met the following inclusion criteria: 1) normal uterine cavity as assessed by ultrasonography, hysterosalpingography, or hysteroscopy; 2) high-quality frozen embryos were transplanted; and 3) the number of ovulation periods antral follicle ranged from 5 to 15. The exclusion criteria were: 1) presence of hydrosalpinges; 2) presence of adenomyosis or endometrioma at the start of the fertility treatment; and 3) polycystic ovary syndrome (PCOS).

The study included 179 patients with stage III–IV endometriosis who underwent 233 FET cycles between March 2011 and August 2013. The control group included 258 patients with tubal factor infertility who underwent 300 FET cycles.

This study was approved by the Ethics Committee of the hospital and conformed to the Declaration of Helsinki (as revised in Tokyo in 2004). The need for individual consent was waived by the committee because of the retrospective nature of the study.

Cryopreservation and thawing

After ovarian stimulation and oocyte retrieval, embryos were produced by IVF or ICSI. Embryos were examined for the number and regularity of blastomeres and the degree of embryonic fragmentation, and were graded according to Cummins's

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criteria [16]. All top-quality embryos (including grades I and II 8-cell blastomere embryos) were vitrified on the third day after oocyte retrieval. The procedure for freezing and thawing cleavage-stage embryos and blastocysts has been described previously [17]. The ovarian stimulation regimen included a short GnRH-a protocol and luteal-phase ovarian stimulation, as described previously [9]. This is in contrast to the currently popular antagonist approach. Frozen embryos with at least 50% of the blastomeres being intact were selected for intrauterine transfer.

FET protocol

For all patients, a modified NC was used for endometrium preparation. A modified NC involves administration of HCG to trigger ovulation. The method for embryo and endometrium synchronization for FET was as follows. Follicular growth was monitored by measuring the levels of serum hormones and performing ultrasound from cycle day 10. When the diameter of the dominant follicle was >16 mm and the endometrial thickness was >8 mm, with estrogen >150 pg/mL and progesterone <1.0 ng/mL, one of two procedures was performed, depending upon the patient's luteinizing hormone (LH) value. If LH was <20 IU/L, 5000 IU of HCG was administered at night (21:00) to trigger ovulation, and the transfer of 3-day-old embryos was performed 5 days later. The quality of the transferred embryos was monitored and was good (grade I and II 8-cell blastomere embryos), as this is vital for a successful outcome. If the LH value was >20 IU/L, 5000 IU HCG was injected the same afternoon, and the embryo transfer was conducted 4 days later. Beginning on the third day after HCG injection, 40 mg of dydrogesterone (Duphaston™, Abbott Laboratories, Abbott Park, IL, USA) was given every day for luteal support. Embryo transfer was performed with ultrasound monitoring. When pregnancy was achieved, the progesterone supplement was continued until 8 weeks of gestation [9].

Collection of data

Patients' characteristics including age, duration of infertility, body mass index, number of embryos transferred, average endometrial thickness of endometrium (mm), basal FSH, serum estrogen and progesterone on the transplantation day, number of previous failed embryo transfer cycles, and rates of basal FSH >10 mIU/mL were recorded.

The main outcomes were the rates of implantation, clinical pregnancy, and live birth. Secondary outcomes were the rates of ongoing pregnancy, miscarriage, and pregnancy complication. Pregnancy was defined as the presence of a gestational sac with fetal heart activity during the ultrasound examination 7 weeks after FET. Implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred. A miscarriage was defined as the loss of pregnancy before 12 weeks of gestation. An ongoing pregnancy was defined as an intact intrauterine pregnancy confirmed by ultrasound at 12 weeks of gestation.

Endometrial cyst recurrence referred to recurrence of an endometrial cyst on the ovary confirmed through vaginal ultrasound after the laparoscopy or laparotomy. The recurrent cyst was ≥2 cm.

Statistical analysis

Statistical analyses were carried out using SPSS 11.0 (SPSS Inc., Chicago, IL, USA). Continuous data with normal distribution are presented as means ± standard deviation (SD) and were analyzed using ANOVA followed by the Student's post hoc test. Categorical data are presented as frequencies and were analyzed using the chi-square test or the Fisher's exact test, as appropriate. Two-sided P-values <0.05 were considered statistically significant.

Results

Characteristics of the patients

Table 1 presents the clinical characteristics of all patients. No significant differences were found in age, duration of infertility, body mass index, number of embryos transferred, average endometrial thickness of ET (mm), basal FSH, rate of FSH >10 mIU/mL, serum estrogen or progesterone levels on the transplantation day, or number of previous failed embryo transfer cycles between the two groups (all P>0.05). Patients with tubal factor infertility group were more likely to have secondary infertility compared to patients with stage III–IV endometriosis (P<0.001). In patients with stage III–IV endometriosis, 40 received 47 FET cycles and had endometrial cyst recurrence after laparoscopic or laparotomy treatment. Data on oocyte retrieval cycles are presented in Table 2.

Treatment outcomes

Treatment outcomes are presented in Table 3. Rates of implantation, clinical pregnancy, and live birth were comparable between the two groups. No differences were found between the two groups in terms of rates of ongoing pregnancy, miscarriage, ectopic pregnancy, or complications. No congenital birth defects were found in the two groups. Patients with stage III–IV endometriosis had smaller babies than patients with tubal factor infertility (median, 2850 *vs.* 3100 g, P=0.001) and delivered earlier (median, 37.0 *vs.* 38.3 weeks, P<0.001).

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Table 1. Characteristics of the patients.

Parameters	Stage III–IV endometriosis		Tubal factor infertility		P
Age	32	(24, 41)	32	(23, 41)	0.395
Body mass index (kg/m^2)	20.58	(15.59, 30.08)	20.56	(15.63, 30.82)	0.385
Duration of infertility (years; [median])	3	(0, 14)	3	(0, 20)	0.315
Infertility type					0
Primary	147	(63.09)	112	(37.33)	
Secondary	86	(36.91)	188	(62.67)	
Basal serum FSH level (mIU/mL)	6.25	(3.2, 22.4)	6.4	(1.4, 22.6)	0.857
FSH >10 (mIU/mL) (%)	41.05		38.95		
FSH ≤10 (mIU/mL) (%)	47.37		36.84		
Number of embryos transferred	2	(1,2)	2	(1, 2)	0.275
One (%)	33	(14.16)	53	(17.67)	
Two (%)	200	(85.84)	247	(82.33)	
Number of previous failed embryo transfer cycles	2	(1,6)	2	(1, 5)	0.433
≤3 (%)	214	(91.85)	289	(96.33)	
>3 (%)	19	(8.15)	11	(3.67)	
Endometrial thickness (mm)	11.3	(5.8, 21.4)	11.1	(5.6, 22.2)	0.689
Serum estrogen levels on transfer day (pg/mL)	91	(15, 309)	98.5	(18, 349)	0.659
Serum progesterone levels on transfer day (ng/mL)	11.3	(2.5, 35)	14.1	(1.0, 35)	0.052

Table 2. Characteristics of the oocyte retrieval cycles.

Characteristics	Stage III–IV endometriosis (n=294)		Tubal infertility (n=305)		P
HMG dose, IU	1884±429		2019±396		<0.001
hMG duration, days	8.8±1.6		9.1±1.7		0.012
No. of >10 mm follicles on the trigger day	10.9±6.8		11.6±6.4		0.159
No. of >14 mm follicles on the trigger day	7.9±6.3		8.5±6.1		0.253
Oocyte retrieval rate, %	67.3%	(2574/3845)	70.2%	(3041/4334)	0.002
Mature oocyte rate, %	87.1%	(2241/2574)	87.2%	(2653/3041)	0.873
Fertilization rate, %	81.0%	(1814/2241)	80.8%	(2143/2653)	0.884
Cleavage rate, %	97.1%	(1742/1814)	96.3%	(2063/2143)	0.132
Viable embryo rate per oocyte retrieved, %	36.5%	(940/2574)	34.7%	(1054/3041)	0.197
High quality embryo rate per oocyte retrieved, %	36.1%	(929/2574)	34.4%	(1047/3041)	0.154
Cancellation rate, %	13.3%	(39/294)	11.2%	(34/305)	0.455

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Table 3. Treatment outcomes.

	Stage III–IV endometriosis 233 cycles		Tubal factor infertility 300 cycles		P
Clinical pregnancy rate (%)	50.2	(117/233)	45.3	(136/300)	0.263
Implantation rate (%)	36.0	(156/433)	30.4	(166/547)	0.06
Ongoing PR (%)	41.6	(97/233)	40.0	(120/300)	0.704
Miscarriage rate (%)	16.2	(19/117)	10.3	(14/136)	0.162
Ectopic pregnancy (%)	0.9	(1/117)	1.5	(2/136)	0.652
Late miscarriage	4		3		
Gestational age (week)	37	(30.71, 41)	38.3	(30.3,41)	0.044
28≤ age <37 (%)	21.5	(20/93)	19.7	(23/117)	0.742
Complications during pregnancy (%)	10.3	(12/117)	12.5	(17/136)	0.577
Live born infants (n)	129		145		
Live birth rate (%)	39.91	(93/233)	39	(117/300)	0.428
Multiple births (%)	27.4	(32/117)	21.3	(29/136)	0.264
Birth weight (g)	2850	(1140, 4100)	3100	(1320, 4450)	0.001
Birth weight <2500 g (%)	26.4	(34/129)	16.6	(24/145)	0.047
Birth height (cm)	50	(40, 53)	50	(40, 53)	0.055
Birth defects (%)	0	(0/129)	0	(0/145)	NA

Table 4. Multivariate analysis for independent factors involved in the clinical pregnancy rate.

	P	OR	95% CI	
Age	<0.001	0.898	0.851	0.948
Body mass index	0.417	0.967	0.89	1.049
Duration of infertility	0.355	1.035	0.962	1.113
Number of embryos transferred	0.030	1.892	1.062	3.369
Number of previous failed embryo transfer cycles	<0.001	0.248	0.187	0.328
Primary or secondary infertility	0.471	1.174	0.759	1.819
Disease groups	0.280	1.265	0.826	1.935

Multivariate analysis for the clinical pregnancy rate

Multivariate analysis revealed that age (OR=0.898, 95%CI: 0.851–0.948, P<0.001), average number of embryos transfer cycles (OR=0.248, 95%CI: 0.187–0.328, P<0.001), and number of embryos transferred (OR=1.892, 95%CI: 1.062–3.369, P=0.030) were independently associated with the pregnancy rate (Table 4).

Outcomes in patients with endometrial cyst recurrence

In addition, the 42 patients with cyst recurrence had 47 FET cycles, leading to a cyst recurrence rate of 23.3%. As shown in Table 5, there were no significant differences in clinical pregnancy (42.55% *vs.* 45.33%) and live birth rates (36.20% *vs.* 39.00%) between stage III–IV endometriosis patients with recurrence of ovarian cyst after laparoscopic treatment and patients with tubal factor infertility. Rates of miscarriage, ectopic pregnancy, and implantation were comparable between the two groups (all P>0.05).

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Table 5. Treatment outcomes of patients with stage III–IV endometriosis with recurrence of endometrial cyst compared with patients with tubal infertility.

	Tubal factor infertility 300 FET cycles		Stage III–IV endometriosis with recurrence of endometrial cyst 47 FET cycles		P
Clinical pregnancy rate (%)	45.33	(136/300)	42.55	(20/47)	0.722
Implantation rate (%)	30.35	(166/547)	33.33	(29/87)	0.575
Ongoing PR (%)	40.0	(120/300)	38.30	(18/47)	0.892
Miscarriage rate (%)	10.29	(14/136)	10.00	(2/20)	0.968
Ectopic pregnancy (%)	1.47	(2/136)	0.85	(0/20)	0.218
Late miscarriage	3		1		0.501
Live born infants(n)	145		23		0.939
Live birth (%)	39	(117/300)	36.17	(17/47)	0.711
Multiple births (%)	21.32	(29/136)	35	(7/20)	0.089

Discussion

While it has been established that many factors are likely to influence the outcome of IVF, such as the adverse roles of nicotine [18] and the methods of preservation of frozen embryos [19], the effects of endometriosis on the results of IVF are currently controversial. Therefore, the aim of the present study was to retrospectively assess the efficacy of NC endometrial preparation for FET in women with severe endometriosis. Results showed that the rates of implantation, pregnancy, and live birth were similar between the two groups. In addition, no differences were observed in the rates of ongoing pregnancy, miscarriage, or pregnancy complications. No congenital birth defects were found. Although severe endometriosis did not affect birth rate, higher frequencies of premature delivery and low birth weight were observed. This effect of severe endometriosis on delivery age and birth weight is supported by a previous study [20], but other studies showed no difference in delivery age or birth weight [21,22]. Because this result could have been affected by the small sample size, additional studies are necessary to address this point.

Some studies reported that infertility of patients with endometriosis was mainly attributed to a reduced ovarian reserve and ovarian response, lower anti-Müllerian hormone levels, higher FSH levels, and abnormal expression of some proteins [10]. In addition, patients with endometriosis showed increased IL-6 secretion, inducing changes in endocrine, paracrine, and autocrine pathways of patients with endometriosis, which probably play a role in the lower implantation rate [23]. The changes observed in women with endometriosis may result in oocytes of low quality and lower ability to implant [24,25]. The follicles also have different steroidogenesis effectiveness between women without and with endometriosis [26]. Serum from patients with endometriosis is embryotoxic for mouse embryos, but this effect can be reversed by glucocorticoid treatment [27]. Furthermore, altered endometrial receptivity in patients with endometriosis may also contribute to endometriosis-associated infertility. A recent meta-analysis revealed that women with endometriosis have a reduced pregnancy rate compared with women with tubal factor infertility [28]. In addition, fertilization and implantation rates have been shown to be different between women with endometriosis-associated infertility and women with tubal factor infertility. Furthermore, a previous study reported that patients with stage III or IV endometriosis have poorer outcomes after assisted reproductive procedures than women with stage I or II endometriosis, indicating that the severity of endometriosis affects the outcome of assisted reproduction [29]. In contrast, Opoien et al. [3] reported that IVF/ICSI carried out in patients with severe endometriosis but without endometrioma achieved outcomes comparable to those with tubal factor infertility. In the present study, patients with endometrioma were not included. Bergendal et al. [30] also found that patients with endometriosis had a reduced response to ovarian stimulation, a lower number of oocytes, and a reduced fertilization rate, but not a reduced pregnancy rate compared with patients with tubal factor infertility.

In the patients with severe endometriosis, there were 294 oocyte retrieval cycles in 271 patients, and 929 top-quality embryos (D3 frozen), and 940 valid embryos (including top-quality embryos and frozen blastocysts) were collected. There were 233 transfer cycles in 179 patients with severe endometriosis. There were 305 oocyte retrieval cycles among 276 patients with tubal factor infertility, and 1047 top-quality embryos (D3 frozen), and 1054 valid embryos (including top-quality embryos

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and frozen blastocysts) were collected. There were 300 transfer cycles in 258 patients with tubal factor infertility. In this study, there were no significant differences in the maturation rate of oocytes, fertilized oocytes, oocyte cleavage rate, top-quality embryos, valid embryos, and cycle cancellation rate.

To the best of our knowledge, few studies have evaluated the pregnancy outcomes after NC-FET in patients with endometriosis. Previous studies have mostly focused on the relationship between fresh embryo transfer and endometriosis and pregnancy outcomes. A previous study reported good outcomes with NC-FET, but it was designed to assess the effect of uterine peristalsis, and no comparisons were made with other approaches [31]. Therefore, the main question of the present study was to determine whether it is feasible to perform FET without pituitary downregulation with a prolonged GnRH-a in patients with endometriosis. Results showed no differences in clinical pregnancy rate between patients with stage III–IV endometriosis and patients with tubal factor infertility. In addition, the rates of implantation and ongoing pregnancy were comparable, but it was lower in patients with endometriosis according to a study by van der Houwen [32]. In this previous study, long-term pituitary downregulation achieved improved ongoing pregnancy rates in IVF-fresh ET, including cryopreserved embryo transfers, compared with NC-FET. In the FET protocols used in our center, only the highest-quality embryos are frozen and transferred, which may have positively affected the outcomes of the study. The present study showed that there was no difference in the miscarriage rate, which is different from a previous meta-analysis [28]. In the present study, a woman with stage III–IV endometriosis underwent labor induction due to general dropsy of the fetus at week 15. In a twin-pregnant woman, one fetus was found with a single umbilical artery, thickening of the neck stratum lucidum, and early embryonic death. Once again, the embryo quality may play a role in this difference. However, the lack of a significant difference could be caused by labor induction due to abnormal results during antenatal examinations, which should be further investigated using larger sample sizes. Results showed that there was no birth defect in the two groups, although fetal abnormalities and abortions were observed during the second trimester. Lack of birth defect could be the result of high-quality embryo transfer, proactive abortion of abnormal fetus through thorough antenatal examinations, or simply because of the limited number of cases in this study. Although severe endometriosis did not affect birth rate, higher frequencies of premature delivery and low birth weight were found, which is supported by previous studies [4,32].

To further investigate the differential effects of FET outcomes by stages of endometriosis, the present study looked at women with severe (stage III or IV) endometriosis and recurrence of ovarian cysts after surgery. Results showed no significant associations between severe endometriosis with recurrence of ovarian cysts and patients with tubal factor infertility after NC-FET. The recurrence of an ovarian cyst represents active endometrial lesions, but the rates of clinical pregnancy and implantation were not significantly affected.

There are several strengths to the present study. First, high-quality embryos were used, which excluded the effect of embryo quality on the implantation rate and pregnancy outcomes in women with severe endometriosis. Since patients with endometriosis often have low-quality oocytes [24], particular care must be taken when selecting the embryos. Second, the effects of down-regulated GnRH-a and high doses of estrogen and progesterone on endometrial receptivity were further excluded. The NC used in the present study was similar to the psychological status, and the effects on endometriosis were slighter. Third, recurrence of endometrial cyst suggests active endometriosis, but the implantation rate was not affected, which means that the endometrial receptivity and the potential of high-quality embryos were not affected. These findings strongly suggest that the effects of endometriosis on fertility could be caused by the environment in the pelvic and abdominal cavities on the quality of the oocytes, which further affected the quality of the embryos, and finally affected the implantation rate and pregnancy outcomes.

Nevertheless, the present study is not without limitations. This was a retrospective study with all the associated biases. A well-designed, prospective, randomized study in severe patients with endometriosis undergoing FET with and without long-term pituitary downregulation should be performed. Another probable bias was that, in the endometriosis group, laparoscopy was not always performed in our hospital, and the severity of the disease had to be determined based on the reports from other hospitals, probably introducing an observer bias.

Conclusions

There was no difference in pregnancy outcomes between patients with endometriosis and those with tubal infertility. Pregnancy outcomes in patients with endometriosis were not affected by endometriosis severity. Pregnancy outcomes were not affected by active endometrial cyst.

Conflict of interests

None.

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