

Original Research Articles

Evaluating the Impact of Long-Term GnRH Agonist Therapy on Pregnancy Outcomes in Endometriosis-Associated Implantation Failure and Pregnancy Loss

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Purpose

This study aimed to investigate the efficacy of long-term gonadotropin-releasing hormone (GnRH) agonist therapy in preventing endometriosis progression and relieving symptoms, particularly on pregnancy outcomes during thawed embryo transfer in patients experiencing endometriosis and recurrent implantation failure or recurrent pregnancy loss.

Methods

In individuals with clinical endometriosis and a history of recurrent implantation failure or recurrent pregnancy loss, we conducted a comparative analysis of clinical outcomes between those undergoing long-term GnRH agonist treatment for symptom relief, such as menstrual pain, followed by embryo transfer using Hormone Replacement Therapy (HRT) cycle, and those undergoing embryo transfer using an HRT cycle without GnRH agonist treatment. The study examined various clinical outcomes between the two groups.

Results

The primary outcomes included live birth rate (LBR), miscarriage rate, biochemical pregnancy rate, and perinatal complications. The GnRH agonist group showed significantly higher LBR than the control group (37.50% vs. 13.04%; $p=0.02$). Multivariable logistic regression analysis, adjusted for age and gravidity, showed significantly higher LBR in the GnRH agonist group compared to the control group (odds ratio: 15.3; 95% confidence interval: 2.30, 102.00; $p=0.005$).

Conclusions

The findings of this study suggested that employing a GnRH agonist in the embryo transfer protocol is effective for patients with endometriosis experiencing recurrent implantation failure or recurrent pregnancy loss.

INTRODUCTION

Endometriosis, affecting approximately 10% of women in their reproductive years,¹ is a condition characterized by pain, notably menstrual cramps and infertility. Nearly half of patients with endometriosis experience infertility, with the disease diagnosed in 20-25% of individuals facing fertility challenges. The fertility rate in women with endometriosis decreases from 0.15-0.2 women/month to 0.02-0.10 women/month.²

Additionally, the likelihood of endometriosis is six to eight times higher in infertile women compared to their fertile counterparts.³ Reported causes of infertility in women with endometriosis encompass luteinized unruptured follicle syndrome, impaired oocyte and embryo formation, endocrine disorders involving luteinizing hormone (LH) surge abnormalities, and ovulation disorders.⁴ Moreover, inflammation in the pelvic region is identified as a potential contributor to these conditions.

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Studies have reported elevated levels of inflammatory cytokines in the pelvic region of individuals with endometriosis.^{5,6} Moreover, studies indicate an increased number of macrophages and cytokines in the peritoneal fluid of women with endometriosis, with this fluid demonstrated to inhibit sperm and oviduct cilia function *in vitro*.⁷

In individuals with endometriosis, elevated concentrations of IL-6 are observed in intraperitoneal reservoir fluid, blood, and follicular fluid. Studies have reported that high IL-6 levels in intraperitoneal fluid can suppress early embryonic development in mice, reduce human sperm motility, and inhibit estrogen production by granulosa cells. These findings imply the involvement of increased cytokines in ascites and blood from individuals with endometriosis in reducing fertility.⁸

Furthermore, the reduced expression of decidualization markers in endometrial tissue from patients with endometriosis, compared to endometriosis-free endometrium, suggests the potential influence of cytokines, increased in ascites fluid, on these markers.⁹ These suggest a potential association between endometriosis and implantation failure.

Increased miscarriage rates have also been reported among patients with endometriosis.^{10,11} Moreover, it has been indicated that a higher miscarriage rate exists among patients with endometriosis compared to those without endometriosis, particularly in cases involving assisted reproductive technology (ART).¹² These findings suggest that patients with endometriosis may exhibit abnormal endometrial conditions due to inflammatory cytokines and other factors, leading to recurrent implantation failure and repeated miscarriages. Furthermore, several studies have reported that GnRH agonist ameliorates pelvic inflammation in endometriosis.^{13,14}

In this study, we retrospectively examined whether the use of GnRH agonists in HRT cycles, with or without embryo transfer, influences the clinical outcomes for patients undergoing ART due to recurrent implantation failure (RIF) (defined as failure to conceive after three or more successful embryo transfers)¹⁵ or recurrent pregnancy loss (RPL) (defined as two or more miscarriages).¹⁶ The primary focus of the retrospective examination was to assess if the use of GnRH agonists during embryo transfers in HRT cycles could bring about changes in the clinical outcome.

METHODS

Seventy patients, all with a history of endometriosis and diagnosed with recurrent implantation failure or recurrent pregnancy loss, were included in this study based on their previous medical history. The clinical outcomes of eligible patients who underwent thawed embryo transfer of frozen blastocysts by HRT cycle in assisted reproductive medicine between April 2022 and December 2022 were retrospectively analyzed. The diagnosis of endometriosis was based on subjective symptoms such as dysmenorrhea, deep dyspareunia, and dysuria, with Beecham Classification stage II or higher considered indicative of clinical endometriosis,

relying on internal examination findings and transvaginal ultrasound.¹⁷

For the purposes of this study, RIF was defined as the inability to achieve pregnancy after three or more embryo transfers involving good blastocysts (Gardner's classification 3BB or higher). RPL was categorized for patients who had encountered two or more previous miscarriages. Ethical approval was obtained from the Ethical Review Committee, and the study was performed on cases where informed consent was obtained from the patients.

For controlled ovarian stimulation, beginning on the first three days of menstruation, either Follitropin alfa (Gonal F; Merck Biopharma, Tokyo, Japan) or Follitropin delta (REKOVELLE; Ferring Pharma, Tokyo, Japan) was used in performing the antagonist or progestin-primed ovarian stimulation (PPOS) method.

Upon reaching approximately 14 mm, the primary follicle triggers the initiation of a GnRH antagonist (Ganirest; MSD, Tokyo, Japan) at a dose of 0.25 mg/day, which was maintained until the primary follicle attained a size of 18–20 mm. The gonadotropin and GnRH antagonist 0.25 mg/day were discontinued upon reaching this size. Simultaneously, on the same day, 250 µg of recombinant hCG (Ovidrel; Merck biopharma) or 600 µg of a GnRH agonist (Suprecur; CLINIGEN, Tokyo, Japan) was administered to trigger oocyte maturation. Oocytes retrieval was performed 34 to 36 hours after the triggering. Oocytes were inseminated with 1 to 5 pre-cultured oocytes at a sperm concentration of 10×10^4 /ml. The following morning (approximately 19 hours post-insemination), oocytes were denuded using an inverted microscope (OLYMPUS IX73, Tokyo, Japan), and a clean bench in the intracytoplasmic sperm injection (ICSI). Sperm collected after swim-up were used in 10% polyvinylpyrrolidone (Irvine Scientific, Santa Ana, U.S.A.) to achieve the optimal concentration. The retrieved oocytes underwent pre-culture and denudation using Cumulus Remover (KITAZATO, Shizuoka, Japan). After ICSI, fertilization was confirmed the next morning (approximately 18 hours post-ICSI). Embryos were cultured individually in ART CULTURE DISH 12 or 24 (nipro, Tokyo, Japan), with 50 µL CSCM-NX per well. Blastocysts were cultured until Day 5/Day 6 and classified as good blastocysts according to Gardner's classification 3BB or higher before undergoing freezing. Vitrification media (KITAZATO) served as the embryo freezing medium, and CRYO-TOP (KITAZATO) as the device.

The GnRH agonist group received depot leuprolide acetate (Leuporelin Acetate; ASKA Pharmacy, Tokyo, Japan) for 1 to 2 months from the 1st to 3rd day of any menstrual period to relieve symptoms such as menstrual cramps associated with endometriosis, then administration of the estrogen preparation (ESTRANA Tapes; Hisamitsu Pharmaceutical, Saga, Japan) 0.72 mg x 4/every other day was started without waiting for the onset of menstruation. Upon confirming endometrial thickness exceeding 7 mm, progesterone drugs (LUTINUS Vaginal Tablets; Ferring Pharma) at 100 mg thrice a day was initiated (P + 0). At six days initiating progesterone drug(P+5), after thawing, the embryos were cultured for 4–6 hours and then trans-

Table 1. Patient Characteristics

Characteristics	GnRH agonist group (n=24)	Control group (n=46)	p-value
Age at oocytes pick up, age	38.04±5.61	35.22±4.38	0.02
Age at embryo transfer, age	38.71±5.92	37.39±4.76	0.31
body weight, kg	58.05 [44.00, 75.00]	57.00 [41.80, 95.00]	0.90
BMI, kg/m ²	23 [18.00, 33.00]	22.5 [17.00, 34.00]	0.50
AMH, ng/ml	2.57 [0.20, 10.99]	3.29 [0.02, 17.64]	0.07
Gravidity, times	1.00 [0.00, 3.00]	1.00 [0.00, 4.00]	0.39
Parity, times	0.00 [0.00, 1.00]	0.00 [0.00, 2.00]	0.009
Number of past embryo transfers, times	4.00 [2.00, 29.00]	4.00 [2.00, 16.00]	0.24
Duration of estrogen supplementation until embryo transfer, days	19.00±2.04	17.93±1.73	0.02
Thickness of the endometrium, mm	9.88±1.36	10.27±1.52	0.29
Serum estradiol level on day of progesterone start, pg/ml	275.12±178.64	299.35±158.23	0.56
Serum progesterone levels on the day of embryo transfer, ng/ml	10.89±2.71	11.64±5.09	0.50
In vitro fertilization (%)	16 (66.70)	20 (43.50)	0.08
Intracytoplasmic sperm injection (%)	8 (33.30)	26 (56.50)	0.08
Blastocyst Quality Score, points	28.83±10.08	31.11±8.53	0.32

Data are presented as mean ± standard deviation or median [Max, min] or n, n (%). The t-test or Mann-Whitney's U test was used for patient characteristics.

ferred under transvaginal ultrasound guidance. In the control group, embryos were transferred without depot leuprolide acetate in HRT cycles initiated on days 1-3 of any menstrual period.

In order to evaluate the effects of GnRH agonist, only patients who underwent embryo transfer during HRT cycles were included in the control group, regardless of menstrual cycle abnormalities or ovulation disorders. Clinical outcomes, including live birth rate, miscarriage rate, biochemical pregnancy rate and perinatal complications, were compared following thawed embryo transfer. In this study, biochemical pregnancies were defined with a cut-off as increasing values of β -hCG > 5 IU/L not confirming fetal sac by transvaginal ultrasonography.¹⁸

Statistical analysis employed a t-test or Mann-Whitney's U test for patient characteristics, with a significance set at a $p < 0.05$. The χ^2 test was used for clinical outcomes, with a significance set at $p < 0.05$.

Additionally, a logistic regression model, adjusted for confounding factors, was used to evaluate the effect of embryo transfer with GnRH agonist on the live birth rate (LBR).

All statistical analyses were performed using EZR (Saitama Medical Center, Saitama, Japan), a software that extends R's capabilities (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 70 patients (GnRH agonist group, n=24; control group, n=46) diagnosed with endometriosis-associated with RIF or RPL were included in the analysis. The demographic characteristics of the women are presented in [Table 1](#). To

facilitate the comparison, the grades of transferred embryos were converted to continuous variables using the Blastocyst Quality Score.¹⁹

Patient characteristics were generally similar between the groups. However, differences were observed in age at oocyte pick-up ($p = 0.02$), parity ($p = 0.009$), and duration of estrogen supplementation until embryo transfer ($p = 0.02$) ([Table 1](#)).

The clinical results indicated that LBR was significantly higher in the GnRH agonist group compared to the control group ($p = 0.02$), and the biochemical pregnancy rate was significantly lower in the GnRH agonist group ([Table 2](#)).

The univariate logistic analysis showed a significant association between LBR and age at oocyte pick-up and gravidity ([Table 3](#)).

In the multiple logistic regression analysis, adjusted for age at oocytes pick up and gravidity, the LBR was significantly higher in the GnRH agonist group than in the control group (odds ratio: 15.3; 95% confidence interval: 2.30, 102.00; $p = 0.005$) ([Table 4](#)).

DISCUSSION

This study suggests that utilizing a GnRH agonist in embryo transfer with HRT cycle may be effective for patients with endometriosis experiencing RIF or RPL. Similar findings have been reported in several previous studies.

Studies have indicated that the long-term use of GnRH agonists prior to *in vitro* fertilization and embryo transfer (IVF-ET) in patients with endometriosis results in significantly higher rates of ongoing pregnancy compared to standard controlled ovarian stimulation regimens.²⁰ Similarly, the long-term use of GnRH agonists before IVF/ICSI in in-

Table 2. Comparison of clinical outcomes.

	GnRH agonist group (n=24)	Control group (n=46)	p-value
Live birth rate (%)	9 (37.50)	6 (13.04)	0.02
Miscarriage rate (%)	0 (0.00)	1 (14.20)	0.47
Biochemical pregnancy rate (%)	0 (0.00)	10 (21.74)	0.01
Perinatal complications (%)	1 (4.20)	0 (0.00)	0.34

The data are presented as n, n (%). The chi-squared test was used to analyze the group difference.

Table 3. Univariate logistic regression analysis for live birth rate.

Variables	Adjusted OR(95%CI)	p-value
Age at oocytes pick up	0.84 (0.74, 0.96)	0.01
Age at embryo transfer	1.02 (0.91, 1.15)	0.68
boy weight	1.03 (0.98, 1.09)	0.26
BMI	1.13 (0.99, 1.29)	0.06
AMH	0.98 (0.79, 1.21)	0.82
Gravidity	0.30(0.12, 0.77)	0.01
Parity	0.25 (0.05, 1.21)	0.09
Number of past embryo transfers	1.07 (0.95, 1.20)	0.27
Duration of estrogen supplementation until embryo transfer	1.17 (0.85, 1.60)	0.32
Thickness of the endometrium	1.17 (0.81, 1.70)	0.41
Serum estradiol level on day of progesterone start	1.00 (0.99, 1.00)	0.70
Serum progesterone levels on the day of embryo transfer	0.97 (0.85, 1.11)	0.67
In vitro fertilization	1.27 (0.41, 4.00)	0.68
Intracytoplasmic sperm injection	1.27 (0.41, 4.00)	0.68
Blastocyst Quality Score	0.98 (0.92, 1.05)	0.61

CI, confidence interval

OR, Odds ratio

Table 4. Multivariable logistic regression analysis results of the two groups and clinical outcomes.

Variables	OR(95%CI)	p-value
GnRH agonist group vs Control group	15.3 (2.3, 102.00)	0.005
Age at oocytes pick up	0.72 (0.58, 0.88)	0.002
Gravidity	0.18 (0.04, 0.70)	0.01

fertile women with endometriosis or adenomyosis has been associated with increased ongoing pregnancy rates in both fresh and frozen cycles.^{21,22}

Possible causes of implantation failure and miscarriage in patients with endometriosis include progesterone (P4) resistance, abnormal expression of integrin (a cell adhesion factor), and overexpression of B-cell lymphoma 6 (BCL6), a biomarker associated with endometriosis.²³ Estrogen receptors (ER- α) in the endometrium, responding to estrogen during the proliferative phase and decreasing during the secretory phase in response to P4, play a crucial role in implantation.²⁴ Suppression of ER- α is important for implantation,²⁵ and P4 is known to promote downregulation of estrogen receptors in the endometrium and promote decidualization.²⁶⁻²⁸ In endometriosis, abnormal expression of

aromatase leads to a local increase in estrogen in the endometrium,²⁹ causing resistance to P4.³⁰ Such abnormalities in estrogen metabolism may affect endometrial receptivity, leading to downregulation of P4 receptors and upregulation of estrogen receptors, resulting in decidualization.³¹ The absence of progesterone receptor B (PR-B), one of the P4 receptor isoforms in endometriosis, has been suggested as a potential cause of these abnormalities in estrogen metabolism.³²

Progesterone receptor (PGR) has isoforms PR-A and PR-B, with PR-A acting as a major repressor of PR-B, whereas PR-B tends to be a more potent activator of P4 target genes.^{33,34} P4 resistance in endometriosis tissue may be explained by the presence of the inhibitory PR isoform PR-A and the absence of the active isoform PR-B.^{35,36} GnRH ag-

onists inhibit aromatase activity in the endometrium, preventing local estrogen increase.³⁷ This effect helps prevents upregulation of estrogen receptors and the active P4 receptor, PR-B, potentially improving decidualization and addressing implantation failure.

Another biomarker indicative of the embryonic receptive state during the implantation phase of the endometrium is the cell adhesion factor integrin, particularly $\alpha\beta3$ integrin. Expression of $\alpha\beta3$ integrin has been linked to implantation failure.³⁸⁻⁴² Moreover, endometriosis has been associated with significantly higher levels of ER- α expression in the mid-secretory endometrium, leading to reduced $\alpha\beta3$ integrin expression.²⁵

The administration of long-acting GnRH agonists prior to treatment has been shown to enhance $\alpha\beta3$ integrin expression in patients with endometriosis, potentially contributing to improved implantation and pregnancy continuation rates.^{22,43}

Patients with endometriosis often exhibit a high levels of BCL6 protein, with a positive predictive value of 96%. BCL6 is a protein encoded by a proto-oncogene located on chromosome 3 (3q27.3) that stimulates inflammatory cytokines, such as IL-6. Inflammation can lead to P4 resistance and abnormal decidualization.⁴⁴ Similarly, overexpression of BCL6 protein is associated with P4 resistance by interfering with P4 signaling, a crucial factor for decidualization.⁴⁵ Studies have reported a significantly lower live birth rate in ART for patients with elevated BCL6 (11.5%) compared to those without elevated BCL6 (58%).⁴⁶

Women suspected of having endometriosis with abnormal endometrial BCL6 expression have demonstrated significantly improved fertility following two months of GnRH agonist or surgical treatment.⁴⁷ These findings suggest that in patients with endometriosis, RIF and RPL may result from P4 resistance due to abnormal estrogen metabolism, decreased integrin expression, and excessive expression of BCL6 protein. The use of GnRH agonist as a premedication for 1-2 months may improve the clinical outcomes for these patients.

Considering that the ESHRE RPL guidelines encompass biochemical pregnancies in the definition of RPL,¹⁶ all patients with implantation failure in this study had experienced at least two biochemical pregnancies, this study suggests that embryo transfer during HRT cycles with GnRH agonist can improve LBR and decrease biochemical pregnancy rate for RPL patients in a broad sense.

LIMITATIONS

The study was conducted with a limited number of patients with uterine infertility, and a notable limitation is that the diagnosis of endometriosis included patients clinically diagnosed according to the Beecham classification,¹⁷ which encompasses a group where a definitive histological diagnosis of endometriosis has not been established. However, in recent years, it is not always necessary to perform laparoscopy and histological examination, as a therapeutic intervention is recommended when clinically suspicious findings of endometriosis are identified during an internal examination or transvaginal ultrasound.⁴⁸⁻⁵⁰ Given the retrospective nature of this study, future prospective studies, with or without prior administration of GnRH agonists in patients with endometriosis, are warranted.

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STATEMENTS AND DECLARATIONS

The authors have no conflicts of interest to declare. All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (facility and national levels) and adhered to the Helsinki Declaration of 1964 and its subsequent amendments. Informed consent was obtained from all patients included in the study. This article does not involve any studies conducted by authors on animal subjects. The protocol for the research project, which includes human subjects, has been approved by the Medical Corporation Kobanawa Clinic Ethic Screening Committee.

COMPETING INTERESTS

The authors have no competing interests to disclose.

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