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Original Article

Modified super-long downregulation protocol improves clinical outcomes of IVF/ICSI-ET in infertile patients with endometriosis

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Abstract: Endometriosis, a common condition in women of reproductive age, has been proven to impair fertility. Prolonged and ultra-long agonist protocols have been shown effective in improving clinical outcomes of IVF/ICSI. The aim of this study was to examine the effectiveness of a modified super-long downregulation protocol (MSDP) on clinical outcomes of IVF/ICSI in patients with endometriosis. Clinical records of a cohort undergoing MSDP and a conventional super-long downregulation protocol (SDP), from October 1, 2013 to February 28, 2016, were retrospectively reviewed. A total of 718 IVF/ICSI cycles were enrolled. IVF/ICSI outcomes were compared between groups. MSDP yielded a significantly higher clinical pregnancy rate (48.6% versus 39%, $P<0.05$), implantation rate (36.1% vs. 27.3%, $P<0.01$), and live birth rate per transfer (41.2% vs. 30.9%, $P<0.05$) than SDP. In endometriosis patients, MSDP also achieved a higher clinical pregnancy rate (56.7% vs. 39.8%, $P<0.05$), implantation rate (38.7% vs. 28%, $P<0.05$), and live birth rate per transfer (46.7% vs. 31%, $P<0.05$). Dosage of gonadotropin administered, duration of gonadotropin administration, fertilization rates, number of high-quality embryos, miscarriage rates, and ectopic pregnancy rates were comparable between endometriosis patients with MSDP and SDP. Results of the present study demonstrate that the MSDP protocol yields better IVF/ICSI outcomes for infertile patients with endometriosis. For infertile women with endometriosis, lacking financial support, the MSDP protocol may provide another treatment option.

Keywords: Endometriosis, controlled ovarian hyperstimulation, modified super-long downregulation protocol, Super-long downregulation protocol, live birth rate

Introduction

Endometriosis is a common and chronic gynecological disorder, affecting 10% to 15% of women of reproductive age [1, 2]. This disorder may be asymptomatic or accompanied by clinical presentations of dyspareunia, chronic pelvic pain, and dysmenorrhea [1]. Strong correlation between endometriosis and infertility has been proven [3-6]. Epidemiologic data shows that 30% to 50 % of women with endometriosis are infertile and 25% to 50% of infertile women have been diagnosed with endometriosis [7-9]. Although several hypotheses have been proposed to explain the correlation between endometriosis and infertility, including distorted pelvic anatomy [10], impaired ovary function [11], altered microenvironment [12], affected endometrial receptivity [13], and reduced oocyte/embryo quality [14-17], the exact pathogenesis of endometriosis-associated infertility has not been completely demonstrated [18-20].

Assisted reproductive technology (ART), notably *in vitro* fertilization (IVF), has been accepted as the most efficient and successful treatment of endometriosis-related infertility [21-23]. A meta-analysis to investigate IVF outcomes in patients with endometriosis indicated a decrease in fertilization and implantation rates and a significant reduction in the number of oocytes retrieved in patients with endometriosis, compared to those with tubal factor infertility [24]. Results from a recent retrospective cohort study, recruiting 22,416 subjects undergoing IVF, showed that women with endometriosis had a

Table 1. Comparison of baseline demographic and clinical characteristics between the SDP and MSDP groups

Characteristics	Group SDP	Group MSDP	*P* value
No. of cycles started	313	405	-
Age (years)	31.65 ± 4.08	31.97 ± 4.49	<0.05
BMI (kg/m^2)	21.2 ± 2.75	21.33 ± 2.91	>0.05
Primary infertility rate	61.3% (187/305)	53.2% (209/393)	<0.05
Duration of infertility (years)	4.38 ± 2.83	4.41 ± 3.01	>0.05
Baseline FSH (IU/L)	7.22 ± 2.34	6.63 ± 1.91	<0.01
Baseline LH (IU/L)	4.25 (3.13-7.35)	4.1 (3.10-5.60)	>0.05
Baseline E_2 (pmol/L)	45.84 (34.13-60.18)	43.62 (33.03-53.22)	>0.05
AFC	14.84 ± 8.17	17.39 ± 8.63	>0.05

BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E_2, estradiol; AFC, antral follicle count; Group SDP, the super-long downregulation protocol group; Group MSDP, the modified super-long downregulation protocol group.

significantly lower number of oocytes retrieved than those without the disease (8.89±6.23 vs. 9.86±7.02, P=0) [25].

In addition to endometriosis, both endometriomas and endometrioma excision have been reported to exhibit detrimental effects on outcomes of IVF due to a reduced number of follicles and oocytes harvested per retrieval [26, 27]. A variety of protocols have been proposed for controlled ovarian hyperstimulation (COH) in IVF and intracytoplasmic sperm injection (IVF/ICSI) treatment [28, 29]. Prolonged pre-IVF cycle suppressive medical therapy, notably gonadotropin releasing hormone agonist (GnRH-a) therapy, has been shown effective in improving clinical outcomes in patients with endometriosis [30-32]. Both prolonged and ultralong GnRH-a therapy before IVF have been found to result in an increase in clinical pregnancy rates in endometriosis patients [33-35]. In addition, a novel modified ultra-long agonist protocol has been reported to achieve better IVF outcomes for polycystic ovary syndrome (PCOS) patients with a high body mass index (BMI), compared to the conventional long agonist protocol [36]. However, there is little known concerning the effectiveness of revised super-long agonist protocols in IVF treatments. The present study compared the efficacy of modified super-long GnRH-a therapy versus a conventional super-long treatment regimen for pregnancy outcomes before IVF/ICSI-ET in infertile patients with endometriosis. The aim was to evaluate the effects of the modified super-long downregulation protocol on clinical outcomes of IVF/ICSI-ET in infertile patients with endometriosis.

Subjects and methods

Ethical statement

This study was approved by the Ethics Review Committee of Fujian Provincial Maternity and Children's Hospital (approval no.: 2016-012). Signed informed consent was obtained from all participants following a detailed description of the purpose of this study.

Study subjects and design

This was a retrospective, non-interventional, and single-center cohort study. A total of 718 IVF/ICSI cycles in 324 infertile patients with endometriosis, undergoing a modified super-long downregulation protocol (MSDP) or conventional super-long downregulation protocol (SDP), in Reproductive Medicine Center of Fujian Provincial Maternity and Children (Fuzhou, China), during the period from October 2013 through February 2016, were enrolled. This study included 313 cycles using the SDP regimen and 405 cycles using the MSDP regimen. Some patients underwent embryos cryopreservation (64 cycles & 68 cycles) for hydrosalpinx, ovarian hyperstimulation syndrome, and hysteromyoma.

Ovarian stimulation and embryo grade

All patients underwent COH using a MSDP or SDP regimen. Conventional SDP regimen was performed by intramuscular injection with long-acting triptorelin (Diphereline, 3.75 mg, IPSEN PHARMA BIOTECH, French) at a dose of 2.5 to 3.75 mg on days 2 to 5 of the cycle. This was followed by intramuscular administration of Gonal-F (Merck Serono Co., Ltd.; Geneva, Switzerland) or Puregon (NV Organon; Oss, the Netherlands) at a daily dose of 150 to 300 IU until the day of human chorionic gonadotrophin (hCG) administration to induce follicular development

Table 2. Comparison of clinical characteristics of patients undergoing controlled ovarian hyperstimulation between the SDP and MSDP groups

Variables	Group SDP	Group MSDP	*P* value
No. of cycles started	313	405	-
No. of cycles with ET	223	311	-
LH on the day prior to Gn administration (mIU/ml)	0.4 (0.20-0.63)	0.3 (0.2-0.4)	<0.01
Dosage of Gn administered (IU)	2430.94 ± 815.22	2723.79 ± 830.95	>0.05
Duration of Gn administration (days)	11.59 ± 2.29	12.72 ± 2.29	>0.05
LH level on the day of hCG administration (mIU/ml)	1.05 (0.3-1.68)	0.90 (0.30-1.30)	<0.01
E_2 on hCG day (pg/ml)	3284.5 (1240.25-4506)	2775.5 (1586.75-4337.5)	>0.05
P concentration on the day of hCG administration (ng/ml)	0.65 (0.4-1.38)	0.7 (0.5-1)	<0.01
Endometrial thickness (mm)	11.58 ± 2.05	11.32 ± 1.85	>0.05
No. of oocytes retrieved	9.9 ± 6.43	9.44 ± 5.86	<0.05
No. of metaphase II stage oocytes	3.23 ± 3.28	3.18 ± 2.92	>0.05
Fertilization rate (%)	81.99 ± 20.4	85.13 ± 18.59	>0.05
No. of high-quality embryos	3.92 ± 3.65	3.78 ± 3.24	>0.05
No. of embryos transferred per ET	1.33 ± 0.87	1.46 ± 0.82	<0.01
No. of cycles cancelled (%)	8/313 (2.56%)	12/405 (2.96%)	>0.05

Group SDP, the super-long downregulation protocol group; Group MSDP, the modified super-long downregulation protocol group; ET, embryo transfer; hCG, human chorionic gonadotropin; LH, luteinizing hormone; Gn, gonadotropin; E_2, estradiol; P, progesterone.

after 4 weeks of pituitary-ovarian suppression. Doses of recombinant follicle-stimulating hormone (FSH) were adjusted according to ovarian response. MSDP regimen was performed by oral administration with Marvelon (NV Organon; Oss, the Netherlands) or Diane-35 (Bayer Schering Pharma AG; Berlin, Germany) from days 2 to 5 of the previous cycle for 21 successive days. The downregulation protocol was performed by administration with long-acting triptorelin at a daily dose of 1.5 to 1.875 mg on days 14 to 19 after administration of an oral contraceptive. This procedure was repeated after 4 weeks. Complete pituitary suppression was confirmed by serum estradiol (E_2) levels <30 pg/mL and serum luteinizing hormone (LH) levels <2 mIU/mL. On days 14 to 20 after pituitary-ovarian suppression, human menopausal gonadotropin (hMG; Livzon Pharmaceutical Group Co., Ltd.; Zhuhai, China) was injected at a daily dose of 112.5 to 375 U until the day of hCG administration. hMG doses were adjusted according to ovarian response assessed by ultrasound and serum E_2 levels. hCG (Livzon Pharmaceutical Group Co., Ltd.; Zhuhai, China) was administered at a dose of 6000~10000 IU to trigger follicular maturation until at least two follicles reached a mean diameter of 18 mm. Oocyte retrieval was performed transvaginally 34 to 36 hours after hCG injection, while ICSI was performed when sperm quality was low on the day of oocytes retrieval or low or infertile in previous cycles. Embryo transfer (ET) was performed under ultrasound guidance 3 days after oocyte retrieval.

Embryos were scored according to cleavage stage, blastomere size, morphology, and fragmentation [37]. Quality of embryos was classified into grades I, II, III, and IV, according to the standard classification system [38]. No more than three Grade I and II embryos were transferred on day 2 or 3 after oocyte retrieval and excessive embryos were cultured and cryopreserved for subsequent frozen embryo transfer (FET) cycles. The luteal phase was supported by intramuscular injections with 60 mg progesterone daily and 10 mg dydrogesterone (10 mg BID; Abbott Biologicals B.V., Veerweg, the Netherlands) from the day of oocyte retrieval. They were adjusted to vaginal progesterone gel 90 mg (Crinone gel 8%; Merck Serono SA; Darmstadt, Germany) once daily and dydrogesterone (10 mg BID; Abbott Biologicals B.V., Veerweg, the Netherlands) from the day of ET. If pregnancy occurred, luteal phase support continued until the 12th week of gestation.

Assessment of pregnancy outcomes

Biochemical pregnancy was defined as serum hCG of >20 IU/L two weeks following ET. Reduced to normal hCG, and clinical pregnancy

Table 3. Comparison of clinical outcomes of IVF/ICSI-ET treatment between the SDP and MSDP groups

Variables	Group SDP	Group MSDP	*P* value
Clinical pregnancy rate per transfer	39.0% (87/223)	48.6% (151/311)	<0.05
Clinical pregnancy rate per started cycle	27.8% (87/313)	37.3% (151/405)	<0.01
Ectopic pregnancy rate	2.3% (2/87)	1.3% (2/151)	>0.05
Miscarriage rate	17.2% (15/87)	13.9% (21/151)	>0.05
Implantation rate	27.3% (111/407)	36.1% (207/574)	<0.01
Live birth rate per transfer	30.9% (69/223)	41.2% (128/311)	<0.05
Premature birth rate per transfer	5.4% (12/223)	7.7% (24/311)	>0.05

Group SDP, the super-long downregulation protocol group; Group MSDP, the modified super-long downregulation protocol group.

Table 4. Comparison of baseline demographic and clinical characteristics between the E-SDP and E-MSDP groups

Characteristics	Group E-SDP	Group E-MSDP	*P* value
No. of cycles started	238	86	-
Age (years)	31.88 ± 3.99	32.66 ± 4.31	>0.05
BMI (kg/m^2)	21.08 ± 2.49	21.06 ± 2.61	>0.05
Primary infertility rate	62.5% (145/232)	66.3% (53/80)	>0.05
Duration of infertility (years)	4.32 ± 2.78	5.24 ± 3.32	>0.05
Baseline FSH (IU/L)	7.28 ± 2.31	6.97 ± 2.02	>0.05
Baseline LH (IU/L)	4.12 ± 2.31	4.43 ± 2.44	>0.05
Baseline E_2 (pmol/L)	47.23 ± 19.2	46.53 ± 17.93	>0.05
AFC	14 ± 7.7	15.76 ± 7.77	>0.05

BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AFC, antral follicle count; E_2, estradiol; AFC, antral follicle count; Group E-SDP, endometriosis patients receiving the super-long downregulation protocol; Group E-MSDP, endometriosis patients receiving the modified super-long downregulation protocol.

was defined as serum hCG of >20 IU/L, confirmed by the presence of a gestational sac according to transvaginal ultrasound scans 5 to 7 weeks after ET. Implantation rate was defined as the number of gestational sacs present on ultrasound scans 5 to 7 weeks after the transfer divided by the number of embryos transferred. Miscarriage rate per clinical pregnancy was defined as the proportion of patients failing to continue development before 28 weeks of gestation in all clinical pregnancies. Live birth was defined as the delivery of a fetus with signs of life after 28 completed weeks of gestation.

Statistical analyses

Normality of data was assessed using a Shapiro-Wilks test. All normally distributed continuous data are expressed as mean ± standard deviation (SD). Abnormally distributed categorical data are described as median (P25, P75), percentages, and numbers. Comparison of quantitative variables was done with Student's *t*-test or Mann-Whitney *U*-test. Differences in qualitative variables were compared with Chi-squared test and Fisher's exact test. All missing data were excluded per test. All statistical analyses were performed using statistical software SPSS version 19.0 (SPSS, Inc.; Chicago, IL, USA). *P* values <0.05 are considered statistically significant.

Results and discussion

Baseline demographic and clinical characteristics of 718 cycles undergoing IVF/ICSI treatments with MSDP and SDP are shown in **Table 1**. There were 698 cycles of oocyte retrieval and 324 cycles with endometriosis. MSDP regimen resulted in a significantly lower primary infertility rate than the SDP regimen (*P*<0.05).

Table 2 displays the differences in COH outcomes and clinical outcomes of IVF/ICSI-ET treatments between SDP and MSDP groups. Dosage of Gn administered, duration of Gn administration, E_2 levels on the day of hCG administration, endometrial thickness, number of high-quality embryos, fertilization rates, ectopic pregnancy rates, miscarriage rates, and premature birth rate per transfer were comparable between the two groups. However, clinical

Table 5. Comparison of clinical characteristics of patients undergoing controlled ovarian hyperstimulation between the E-SDP and E-MSDP groups

Variables	Group E-SDP	Group E-MSDP	*P* value
No. of cycles with ET	171	60	-
LH on the day prior to Gn (mIU/ml)	0.4 (0.3-0.9)	0.3 (0.2-0.4)	>0.05
Dosage of Gn (IU)	2433.14 ± 791.07	2886.09 ± 789.53	>0.05
Duration of Gn administration (days)	11.49 ± 2.16	12.55 ± 2.23	>0.05
LH level on the day of hCG administration (mIU/ml)	1.3 (0.6-2.55)	0.9 (0.5-1.2)	<0.01
E_2 level on the day of hCG administration (pg/ml)	3283.34 ± 2270.43	2938.74 ± 2075.53	>0.05
P concentration on the day of hCG administration (ng/ml)	0.9 (0.6-1.4)	0.6 (0.4-0.9)	<0.01
Endometrial thickness (mm)	11.67 ± 2.13	11.38 ± 1.77	>0.05
No. of oocytes retrieved	9.84 ± 6.4	8.9 ± 5.56	>0.05
No. of metaphase II stage oocytes	3.18 ± 3.11	2.99 ± 2.4	<0.05
Fertilization rate (%)	81.45 ± 20.83	84.87 ± 18.31	>0.05
No. of high-quality embryos	3.96 ± 3.7	3.81 ± 3.46	>0.05
No. of embryos transferred per ET	1.34 ± 0.87	1.39 ± 0.86	>0.05
No. of cycles cancelled (%)	6/238 (2.5%)	6/86 (7.0%)	>0.05

ET, embryo transfer; hCG, human chorionic gonadotropin; LH, luteinizing hormone; Gn, gonadotropin; E_2, estradiol; P, progesterone; Group E-SDP, endometriosis patients receiving the super-long downregulation protocol; Group E-MSDP, endometriosis patients receiving the modified super-long downregulation protocol.

Table 6. Comparison of clinical outcomes of IVF/ICSI-ET treatment between the E-SDP and E-MSDP groups

Variables	Group E-SDP	Group E-MSDP	*P* value
Clinical pregnancy rate per transfer	39.8% (68/171)	56.7% (34/60)	<0.05
Ectopic pregnancy rate	2.9% (2/68)	2.9% (1/34)	>0.05
Miscarriage rate	17.6% (12/68)	14.7% (5/34)	>0.05
Implantation rate	28% (87/311)	38.7% (43/111)	<0.05
Live birth rate per transfer	31% (53/171)	46.7% (28/60)	<0.05
Premature birth rate per transfer	5.3% (9/171)	3.3% (2/60)	>0.05

Group E-SDP, endometriosis patients receiving the super-long downregulation protocol; Group E-MSDP, endometriosis patients receiving the modified super-long downregulation protocol.

pregnancy rate per transfer, clinical pregnancy rate per started cycle, implantation rates, and live birth rate per transfer were greater in the MSDP group than SDP group (*P*<0.05 or 0.01). (**Table 3**).

Baseline demographic and clinical features were not significant between endometriosis patients with MSDP and SDP (**Table 4**). Endometriosis patients with SDP had higher LH levels on the day of hCG administration, higher progesterone concentrations on the day of hCG administration, and more metaphase II stage oocytes than those with MSDP (*P*<0.05 or 0.01). However, no significant differences were detected in terms of LH on the day prior to Gn administration, dosage of Gn, duration of Gn administration, E_2 levels on the day of hCG administration, endometrial thickness, number of oocytes retrieved, fertilization rates, number of high-quality embryos, number of embryos transferred per ET, and number of cycles cancelled (*P*>0.05) (**Table 5**). Following IVF/ICSI-ET treatments, endometriosis patients with SDP had lower clinical pregnancy rate per transfer, implantation rates, and live birth rate per transfer than those with MSDP (*P*<0.05). No significant differences were observed in ectopic pregnancy rates, miscarriage rates, or premature birth rate per transfer (*P*>0.05) (**Table 6**).

In the present study, a modified super-long downregulation protocol, characterized by two desensitization treatments and administration of urinary hMG, was introduced. This protocol resulted in clear improvement of IVF/ICSI outcomes in patients with endometriosis. Endometriosis has shown adverse effects on various aspects of reproductive physiology [4] and has

been closely associated with infertility [4-6]. However, causes of endometriosis-associated infertility have not been completely demonstrated [18-20].

Currently, management of endometriosis-related infertility remains controversial [39, 40]. Different treatment options have been proposed, mainly depending on the severity of endometriosis and presence or absence of endometriomas [41]. In our center, there are three major protocols used to manage endometriosis-related infertility. These include a GnRH-a downregulation protocol, GnRH antagonist downregulation protocol, and pretreatment with oral contraceptives alone or in combination with surgical intervention.

In the modified super-long downregulation protocol, double desensitization treatments may suppress serum LH to extremely low levels. It should be noted that low initial LH concentration might impair E_2 synthesis [32]. Supplem enting LH may provide a solution. Urinary hMG, containing 75 IU LH and 75 IU FSH, was administered as an alternative of conventional rhFSH. This modification yielded a higher peak E_2 concentration compared to the conventional super-long downregulation protocol (3284.5 vs. 2775.5, $P<0.05$), indicating that the modified super-long downregulation protocol did not affect E_2 synthesis through administration of urinary hMG. In addition, the price of urinary hMG is much lower than rhFSH, greatly reducing medical costs during COH.

In the current study, endometrial thickness and number of high-quality embryos were comparable between the two protocols. However, lower progesterone concentrations were detected on the day of hCG administration in endometriosis subjects using MSDP, compared to those using SDP. This may have a great negative affect on endometrial receptivity [33-35]. These findings suggest that the modified super-long downregulation protocol depresses progesterone during COH. The duration of Gn administration was longer in the E-MSDP group than E-SDP group. Prolonged downregulation is active against endometriosis. This may explain why the modified super-long downregulation protocol achieves better clinical outcomes in IVF/ICSI.

The present study had some limitations. First, patients with endometriosis were not staged. Second, this was a retrospective study. Further large-scale prospective, randomized, and controlled clinical trials will be necessary to validate the findings from this study.

In summary, results of the present study demonstrate that the modified super-long downregulation protocol yields better IVF/ICSI outcomes for infertile patients with endometriosis. For infertile women with endometriosis lacking financial support, this modified super-long downregulation protocol may provide another treatment option.

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Disclosure of conflict of interest

None.

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