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ScienceDirect

Journal of the Chinese Medical Association 77 (2014) 524–530

www.jcma-online.com

Original Article

Luteal phase support with decapeptyl improves pregnancy outcomes in intracytoplasmic sperm injection with higher basal follicle-stimulating hormone or lower mature oocytes

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Received January 8, 2014; accepted February 27, 2014

Abstract

Background: The role of midluteal phase gonadotropin-releasing hormone (GnRH) agonist had been an issue of debate. The aim of this retrospective study was to evaluate the effect of a mid-luteal phase GnRH agonist as an additional luteal phase support (LPS) in patients receiving intracytoplasmic sperm injection (ICSI). Additionally, we elucidate which subgroup would gain the most benefit from GnRH agonist as LPS.

Methods: The medical records were retrieved from January 2009 to January 2012 and a total of 348 patients receiving ICSI were included in this retrospective study. Among them, 240 patients met the inclusion criteria of patients aged ≤38 years, previous assisted reproductive technology (ART) cycles ≤ 2. There were 147 patients in the decapeptyl group who received GnRH agonist decapeptyl 6 days after ICSI as additional LPS and 93 patients in the control group. Subgroupings were done according to advanced age, the number of previous ART cycles, high basal follicle-stimulating hormone (FSH) level, and patients who had fewer mature oocytes retrieved. Live birth rates, clinical pregnancy rate (CPR), and implantation rate were the primary outcomes.

Results: LPS with decapeptyl led to a higher implantation rate (24.5% vs. 17.0%, $p = 0.023$), a higher CPR (49.0%, $n = 72$ vs. 33.3%, $n = 31$, $p = 0.023$) and a higher live birth rate (41.5%, $n = 61$ vs. 28.0%, $n = 26$, $p = 0.039$). In the subgroup analysis, decapeptyl improved the CPR of those patients with basal FSH >8 mIU/mL (50.0%, $n = 15$ vs. 8.3%, $n = 1$, $p = 0.031$) and also improved CPR (42.3%, $n = 11$ vs. 0%, $n = 0$, $p = 0.017$) and live birth rate (30.8%, $n = 8$ vs. 0%, $n = 0$, $p = 0.035$) of patients whose number of mature oocytes was three or fewer.

Conclusion: This study demonstrated that administration of decapeptyl as additional luteal support can enhance ICSI clinical outcomes. Those patients with higher basal FSH level or fewer number of mature oocytes may obtain particularly significant benefit.

Keywords: assisted reproductive technologies; decapeptyl; luteal phase support

1. Introduction

Luteal phase defect is common in follicular stimulation using assisted reproductive technologies (ARTs), with either a downregulated gonadotropin-releasing hormone (GnRH) agonist protocol followed by human menopausal gonadotropin (hMG)/follicle-stimulating hormone (FSH) or a GnRH antagonist protocol with hMG/FSH. Luteal phase support

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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http://dx.doi.org/10.1016/j.jcma.2014.07.001

(LPS) is therefore a common practice in infertility treatment to improve the implantation rate, clinical pregnancy rate (CPR), and delivery rate. LPS with intramuscularly administered human chorionic gonadotropin (hCG) and intramuscular progesterone significantly improve fertility outcomes.[1] Some studies reported vaginal progesterone gel can be successfully used as an alternative to intramuscular progesterone for luteal support and even results in better pregnancy outcomes than intramuscular progesterone.[2] Fatemi also found that the addition of estradiol (E2) seems to be beneficial in long GnRH agonist protocol.[3] In 2004, Tesarik et al[4] designed a retrospective controlled study and demonstrated that GnRH agonist as LPS in intracytoplasmic sperm injection (ICSI) cycles improved implantation (36.9% vs. 25.1%) and birth (31.1% vs. 25.1%). Thereafter a number of studies confirmed the effect of GnRH agonist as LPS. In 2010, a meta-analysis presented significantly higher rates of implantation, CPR per transfer, and ongoing pregnancy in the group that received a single dose of GnRH agonist at Day 5/6 after ICSI procedures than in the control group.[5] In 2011, a Cochrane review demonstrated a significant effect in favor of progesterone + GnRH agonist versus progesterone for live birth, CPR, and ongoing pregnancy rate.[6] These findings demonstrate that the GnRH agonist as LPS is beneficial for pregnancy outcomes. Nevertheless, concerning the heterogeneity between the trials, the usage of GnRH agonist in the luteal phase remains a current topic of debate. In this study, we conducted a retrospective analysis to evaluate the effect of a single injection of GnRH agonist 6 days after oocyte retrieval as LPS in ICSI cycles. Furthermore, in current practice LPS with GnRH agonist remained an optional treatment. As a booster to enhance the likelihood of a positive result, knowledge about how to select the right patient for such a treatment is still lacking. There is currently no clear guideline regarding patient selection for LPS with GnRH agonist. As such, the secondary objective was to conduct a subgroup analysis in the study population to find out which subgroup of patients would gain the most benefit from such a treatment. The primary outcomes are implantation rates, CPR, and live birth rates.

2. Methods

2.1. Research design and study population

We used a retrospective design in this study, aimed at evaluating the effect of GnRH agonist (triptorelin; decapeptyl 0.1 mg, Ipsen Pharma, Barcelona, Spain) to support the luteal phase in patients undergoing ICSI. To be enrolled in this study, couples had to be undergoing ART with their own gametes and have at least one embryo available for transfer. In addition, patients who received ICSI cycles had to be stimulated with either traditional long or antagonist protocol. Female patients aged ≥38 years, with more than two previous *in vitro* fertilization cycles were excluded. General health status was assessed, including tests for human immunodeficiency virus and syphilis.

We examined the clinical information of 607 infertile couples recorded between January 2009 and January 2012. Through the selection criteria, a total of 240 patients undergoing ICSI were identified.

There were 147 patients in the decapeptyl group and 93 patients in the control group. Informed consent was obtained from all patients for the use of decapeptyl. There were 183 patients who underwent a long GnRH agonist protocol and 57 patients used GnRH antagonist protocol.

Those who received decapeptyl as luteal support were designated as the decapeptyl group and informed consent for the usage of decapeptyl was preserved and confirmed; those who did not receive decapeptyl were deemed the control group. This study was approved by the Institutional Review Board or Ethics Committee of Taichung Veterans General Hospital, Taichung, Taiwan.

The women in the decapeptyl group received a single subcutaneous injection of 0.1 mg triptorelin (decapeptyl 0.1 mg) 6 days after ICSI. According to the chart information, both groups were given progesterone as luteal support. The live birth rate, CPR, and implantation rate were recorded as primary outcomes. The patients were subgrouped according to poor risk factors such as advanced age, more previous ART cycles, higher basal FSH level, and patients with fewer mature oocytes retrieved. Subgrouping according to ovarian stimulation protocol was also done.

2.2. Stimulation protocols

2.2.1. Long GnRH agonist protocol

Leuprolide acetate (Leupron; Takeda Pharmaceuticals, Osaka, Japan) or triptorelin (decapeptyl 0.1 mg; Ipsen Pharma, Barcelona, Spain) was administered subcutaneously at a daily dose of 0.1 mg starting in the luteal phase of the cycle preceding controlled ovarian hyperstimulation (COH) and reduced to a 0.05 mg daily dose on the day of ovarian stimulation. Either leuprolide or triptorelin was stopped on the days of hCG administration. Stimulation was started on Days 3−5 of the cycle with the use of recombinant FSH (Puregon; MSD, Oss, The Netherlands or Gonal F; Merck Serono, Geneva, Switzerland) and/or HMG (Menopur; Ferring SAS, St. Prex, Switzerland).

2.2.2. GnRH antagonist protocol

Recombinant human FSH (Gonal-F, Serono Laboratories, Aubonne, Switzerland) or HMG administration was started on Day 2 or Day 3 of the period. GnRH antagonist (Ganirelix; Orgalutron, Organon, The Netherlands or Cetrotide; Serono, Germany) was started with a leading follicle ≥ 14 mm, at a daily dose of 0.25 mg, and continued until the day of hCG administration.

In general, long GnRH agonist protocols are reserved for younger patients and better ovarian response except for ovarian hyperstimulation syndrome (OHSS) and GnRH antagonist are reserved for older patients and poor responders. In the aforementioned protocols, basal serum FSH, luteinizing hormone, and E2 were measured on Days 2−5 of the cycle preceding ovarian stimulation. Serial transvaginal ultrasound was performed to monitor the follicular growth and the dose of FSH and

HMG were adapted according to the dynamics of follicular growth. The endometrial thickness and serum LH, E2, and progesterone were assessed on the day of hCG administration. Ovulation was induced with 500 μg recombinant human chorionic gonadotropin (rhCG) (Ovidrel, Serono, Germany) when at least three follicles reached a mean diameter of 18 mm. Transvaginal ultrasound-guided oocyte retrieval was undertaken 35–36 hours after the administration of hCG. Fertilization was achieved with ICSI in all cases. Basic sperm parameters (sperm count, motility, and morphology) were recorded on the day of ICSI. Retrieved oocytes were labeled as mature by the characteristics of well-expanded cumulus, the appearance of corona radiata, the first polar body, and clear ooplasm. Embryo transfer was performed 3–5 days after oocyte retrieval. The number of embryos transferred was from one to four depending on age, number of attempts, embryo quality, and patient choice. All women received LPS with vaginal progesterone gel 90 mg/day 8% (Crinone; Merck Serono) or intramuscular progesterone 25–50 mg/day starting on the day of oocyte retrieval. Decapeptyl was offered as an optional choice in all patients undergoing ICSI. Informed consent was obtained from the patients who agreed with the self-pay medication and an additional single dose of 0.1 mg decapeptyl was given on Day 6 after ICSI. LPS was continued until the serum β-hCG was assessed 14 days after oocyte retrieval. Women with a positive pregnancy test continued the LPS until the 8th week of gestation.

2.3. Outcome measures

Pregnancy was first assessed 14 days after oocyte retrieval by determining serum β-hCG, and the gestational sac was confirmed 3 weeks later by transvaginal ultrasound. Clinical pregnancies were characterized by the presence of at least one intrauterine gestational sac with detectable heartbeat 4 weeks later. Clinical pregnancy rate was calculated as the number of patients showing a clinical pregnancy divided by the number of embryo transfer procedures. Live birth rates were calculated as the percentage of ART cycles started that resulted in a live birth. The birth of more than one baby was counted as one live birth. Implantation rates were calculated by dividing the number of gestational sacs with heartbeat by the number of embryos transferred.

2.3.1. Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation, number (percentage), or median (interquartile range), and analyzed using the Student t test, Chi-square test, or Fisher's exact test, and Yates correction for continuity as appropriate. A p value of <0.05 was considered statistically significant.

3. Results

The demographic characteristics of the enrolled couples are summarized in Table 1. No differences were found in age ($p = 0.274$), body mass index ($p = 0.475$), duration of infertility ($p = 0.929$), number of previous ART cycles ($p = 0.129$), obstetric history (see Table S1 in the supplementary material online), and the main cause of infertility between groups. The basal FSH level on the day of ovarian stimulation was significantly higher in the decapeptyl group than the control group (4.36 vs. 3.79, $p = 0.024$). Cycle characteristics of the couples and the pregnancy outcomes are summarized in Table 2. No differences were found in the total COH duration (10.08 ± 1.61 vs. 10.10 ± 1.45, $p = 0.948$), total FSH consumption (2172.00 ± 678.75 vs. 2054.25 ± 588.75, $p = 0.177$) and endometrial thickness on day of rhCG administration (11.88 ± 2.19 vs. 11.52 ± 2.31, $p = 0.235$). There was a higher level of progesterone on hCG day in the decapeptyl group (1.24 ng/mL vs. 0.94 ng/mL, $p = 0.005$). However, the percentage of patients with progesterone level on hCG day >1.5 ng/mL was not significantly different between groups (21.7% vs. 11.8%, $p = 0.122$). The incidence of OHSS was not different between groups (2.7% vs. 4.3%, $p = 0.794$). Concerning the stimulation protocol, more patients used antagonist protocol in the decapeptyl group than the control group (30.7%, $n = 45$ vs. 13.0%, $n = 12$, $p = 0.001$), combined with the basal FSH, suggesting that the decapeptyl group may have poorer ovarian response. Importantly, although female patients in the decapeptyl group had fewer mature oocytes retrieved (8.81 ± 5.30 vs. 11.56 ± 7.41, $p = 0.001$) and fertilized eggs (6.69 ± 4.46 vs. 8.55 ± 5.98, $p = 0.001$), the female patients in the decapeptyl group had higher rates of clinical pregnancy (49.0% vs. 33.3%, $p = 0.023$), implantation rate (24.5% vs.17.0%, $p = 0.023$)

Table 1
Demographics of patients aged ≤ 38 years and with fewer than two previous failure attempts who underwent intracytoplasmic sperm injection treatment with or without decapeptyl as additional luteal support.

	Decapeptyl group ($n = 147$)	Control group ($n = 93$)	p
Age of patients [y] (SD)	34.11 (3.35)	33.57 (4.02)	0.274[a]
Age of husband [y] (SD)	36.57 (4.36)	36.42 (5.07)	0.808[a]
Body mass index [kg/m^2] (SD)	22.19 (3.11)	21.25 (2.61)	0.475[a]
Basal FSH [IU/L] (SD)	4.36 (2.08)	3.79 (1.57)	0.024*[a]
Duration of infertility [y] (SD)	4.03 (2.92)	4.00 (2.74)	0.929[a]
Main cause of infertility, n (%)			
Tubal factor	27 (18.4)	17 (18.3)	0.861[b]
Endometriosis	45 (30.6)	19 (20.4)	0.100[b]
Adenomyosis	5 (3.4)	2 (2.2)	0.867[c]
PCOS	6 (4.1)	3 (3.2)	1[c]
Cancer	2 (1.4)	0 (0)	0.689[c]
Multiple factors	1 (0.8)	0 (0.3)	1[c]
Unexplained factor	3 (2.0)	7 (7.5)	0.082[c]
Male factor	90 (61.2)	51 (54.8)	0.348[b]
Primary infertility	102 (69.9)	60 (64.5)	0.398[b]
No. of previous ART cycles [mean]	0.67	0.53	0.129[a]

*$p < 0.05$.
ART = assisted reproductive technology; FSH = follicle-stimulating hormone; PCOS = polycystic ovary syndrome; SD = standard deviation.
[a] Student t test.
[b] Fisher's exact test.
[c] Yates' correction of contingency.

Table 2
Cycle characteristics and pregnancy outcomes.

	Decapeptyl group ($n = 147$)	Control group ($n = 93$)	p
Stimulation protocol			0.001*,[d]
Long protocol	102 (69.3)	81 (87.0)	
Antagonsit protocol	45 (30.7)	12 (13.0)	
Total COH duration, d (SD)	10.08 (1.61)	10.10 (1.45)	0.948[a]
Total FSH consumption, IU (SD)	2172.00 (678.75)	2054.25 (588.75)	0.177[a]
Endometrial thickness, mm (SD)	11.88 (2.19)	11.52 (2.31)	0.235[a]
Progesterone level on HCG day, ng/mL (SD)[e]	1.24 (0.77)	0.94 (0.44)	0.005[a]
Progesterone on HCG day level > 1.5 ng/mL	32 (21.7)	11 (11.8)	0.122[b]
No. of mature oocytes retrieved	8.81 (5.30)	11.56 (7.41)	0.001*,[a]
No. of fertilized oocytes	6.69 (4.46)	8.55 (5.98)	0.011*,[a]
No. of embryos transferred	2.98 (0.99)	3.08 (0.96)	0.376[a]
Cinical pregnancy	72 (49.0)	31 (33.3)	0.023*,[b]
Live birth	61 (41.5)	26 (28.0)	0.039*,[b]
Implantation rate	0.245	0.17	0.023*,[a]
OHSS	4 (2.7)	4 (4.3)	0.794[c]

Data are presented as n (%), unless otherwise indicated.
*$p < 0.05$.
COH = controlled ovarian hyperstimulation; OHSS = ovarian hyperstimulation syndrome; SD = standard deviation.
[a] Student t test.
[b] Fisher's exact test.
[c] Yates' correction of contingency.
[d] Pearson χ^2 test.
[e] Progesterone level: progesterone level at the day of HCG (Day 0).

and live birth rate (41.5% vs. 28.0%, $p = 0.039$) than in the control group.

Further subgroup analysis of patients aged ≤38 years who had no more than two previous cycles revealed significant benefit in certain unfavorable conditions (Tables 3 and 4). First, patients with basal FSH > 8 mIU/mL in the decapeptyl group had higher live birth rates than those in the control group (50%, $n = 15$ vs. 8.3%, $n = 1$, $p = 0.031$). Second, patients with no more than three mature oocytes had significantly higher clinical pregnancy rates (42.3%, $n = 11$ vs.0%, $n = 0$, $p = 0.017$) and live birth rates (30.8%, $n = 8$ vs. 0%, $n = 0$, $p = 0.035$). On the contrary, according to another substudy using different exclusion criteria, in patients with advanced age (>38 years) and more previous ART attempts (>2 previous cycles) LPS with decapeptyl did not provide a better result (see Tables S2 and S3 in the supplementary material online). Subgrouping according to stimulation protocol showed that LPS with decapeptyl is associated with a significantly higher clinical pregnancy rate (50.0% vs. 27.0%, $p = 0.025$) and live birth rate (42.9% vs. 21.6%, $p = 0.035$) when a short protocol was used for ovary stimulation. When a long protocol was used, patients in the decapeptyl group still had a higher clinical pregnancy rate (48.1% vs. 37.5%, $p = 0.288$) and live birth rate (40.3% vs. 32.1%, $p = 0.367$) but without statistical significance (Table 5).

Table 3
Subgroups according to patient's basal follicle stimulating hormone (cycles ≤ 2, patient's age ≤ 38 years).

a. Basal FSH > 8 mIU/mL			
	Decapeptyl group ($n = 30$)	Control group ($n = 12$)	p
Clinical pregnancy	15 (50)	1 (8.3)	0.031*,[c]
Live birth	10 (33.3)	1 (8.3)	0.096[c]
No. of mature oocytes retrieved	3.48 (1.92)	8.5 (7.23)	0.003*,[d]
No. of fertilized oocytes	2.6 (1.63)	6.3 (7.04)	0.017*,[d]
b. Basal FSH ≤ 8 mIU/mL			
	Decapeptyl group ($n = 117$)	Control group ($n = 81$)	p
Clinical pregnancy	57 (48.7)	30 (37.0)	0.064[b]
Live birth	51 (43.6)	25 (30.8)	0.133[b]
No. of mature oocytes retrieved	9.94 (5.29)	12.12 (7.53)	0.007*,[a]
No. of fertilized oocytes	7.52 (4.36)	8.89 (5.84)	0.07[a]

Data are presented as n (%).
*$p < 0.05$.
[a] Student t test.
[b] Fisher's exact test.
[c] Yates' correction of contingency.
[d] Mann–Whitney U test.

4. Discussion

Luteal phase defect has been a well-known problem in ARTs. Many studies have proposed the positive effect of GnRH agonist as LPS. GnRH agonist was once thought to interfere with implantation and cause luteolysis, resulting in a contraceptive effect.[7,8] In 1990, Loumaye[9] proposed that GnRH agonist may

Table 4
Subgroups according to the number of mature oocytes (cycles ≤ 2, patient age ≤ 38 years).

Number of mature oocytes ≤ 3			
	Decapeptyl group ($n = 26$)	Control group ($n = 13$)	p
Clinical pregnancy	11 (42.3)	0 (0)	0.017*,[c]
Live birth	8 (30.8)	0 (0)	0.035*,[b]
No. of mature oocytes retrieved	2.19 (0.66)	2.46 (0.75)	0.279[d]
No. of fertilized oocytes	1.88 (0.77)	1.92 (0.95)	0.892[d]
Number of mature oocytes > 3			
	Decapeptyl group ($n = 121$)	Control group ($n = 80$)	p
Clinical pregnancy	61 (50.4)	31 (38.8)	0.114[b]
Live birth	53 (43.8)	26 (32.5)	0.140[b]
No. of mature oocytes retrieved	10.27 (4.95)	13.24 (7.06)	0.01*,[a]
No. of fertilized oocytes	7.71 (4.21)	9.7 (5.76)	0.052[a]

Data are presented as n (%).
*$p < 0.05$.
[a] Student t test.
[b] Fisher's exact test.
[c] Yates' correction of contingency.
[d] Mann–Whitney U test.

Table 5
Subgroups according to stimulation protocol (cycles ≤ 2, patient age ≤ 38 years).

Long protocol			
	Decapeptyl group (n = 77)	Control group (n = 56)	p
Clinical pregnancy	37 (48.1)	21 (37.5)	0.288[a]
Live birth	31 (40.3)	18 (32.1)	0.367[a]
Short protocol			
	Decapeptyl group (n = 70)	Control group (n = 37)	P
Clinical pregnancy	35 (50)	10 (27.0)	0.025*,[a]
Live birth	30 (42.9)	8 (21.6)	0.035*,[a]

Data are presented as n (%).
*$p < 0.05$.
[a] Fisher's exact test.

suppress pituitary function and induced desensitization of pituitary gonadotroph cells. Furthermore, Herman et al[10] reported deterioration of corpus luteum with the administration of GnRH agonist. By contrast, since 1993 a series of studies have revealed that inadvertent administration of a GnRH agonist does not compromise pregnancy outcomes, but instead enhances implantation.[11–16] In 2004, a study conducted by Tesarik et al[4] demonstrated that administration of 0.1 mg triptorelin 6 days after ICSI in an oocyte donation program enhanced embryo development potential. In addition, there was a significant trend toward an improvement in clinical pregnancy (31.1% vs. 21.5%) and implantation rates (36.9% vs. 25.1%) and serum β-hCG levels in the decapeptyl group. Although recently some authors have suggested that administration of a GnRH agonist in the luteal phase has a beneficial effect on ART outcomes,[4,17] other authors did not confirm such a benefit from the administration of a GnRH agonist in the luteal phase.[18–20] Furthermore, the detailed mechanisms of the presumed possible benefits of luteal-phase GnRH agonists remained unclear. In addition, as we know there are several causes of human infertility, there are still many questions to be answered: Does every patient benefit from such a treatment? Will all the poor risk patients gain benefit? If not, what type of patient will benefit from LPS with GnRH agonist?

In our study, we adopted the regimen described by Tesarik et al[34] and analyzed the effect of 0.1 mg decapeptyl administered 6 days after ICSI as luteal support on clinical pregnancy outcomes. We selected younger female patients (aged ≤ 38 years) who had fewer previous cycles (≤2). The first finding of this study was that decapeptyl was beneficial in ICSI outcomes including higher pregnancy rates (49.0% vs. 33.3%), live birth rates (41.5% vs. 28.0%), and implantation rates (24.5% vs. 17%) although the patients in the decapeptyl group had poorer ovarian response than those in the control group (as revealed by higher basal FSH level, reduced number of mature oocytes retrieved, and fertilized eggs). The subgroup analysis in the same group of female patients according to basal FSH found that patients with poorer basal FSH > 8 mIU/mL had a higher live birth rate. The second subgroup analysis according to mature oocytes found that three or fewer mature oocytes showed significant benefit from decapeptyl. This may indicate that decapeptyl as LPS may be recommended not only for patients undergoing ICSI, but also should be strongly suggested for patients with higher basal FSH levels and fewer mature oocytes. As indicated in Tables 3 and 4, with LPS using decapeptyl those patients with basal FSH > 8 mIU/mL or three or fewer mature oocytes can achieve almost the same CPR and live birth rate as patients of FSH ≤ 8 mIU/mL or more than three mature oocytes.

However, in 2008 a randomized controlled study by Ata et al[21] showed that LPS with GnRH agonist did not offer better results when long protocol was used for ovary stimulation. In 2012, another randomized trial by Inamdar et al[22] also showed the same result. It was thought that downregulation of GnRH receptors by GnRH agonist in a long protocol may offset the effect of luteal phase GnRH agonist. Our study also showed the same tendency that the benefit of luteal phase GnRH agonist was significant only when a short protocol was used (Table 5).

Because a short protocol was mainly used for those patients with poor ovarian response, the benefit those patients with high basal FSH level and few mature oocytes had gained (Tables 3 and 4) could be attributable to their short stimulation protocol. To clarify this point, we further stratify the subgroups of high basal FSH level and few mature oocytes by stimulation protocol. Although the sample size is too small to achieve statistical significance, those patients with few mature oocytes had improved CPR and live birth rates under GnRH agonist LPS even when a long protocol was used (see Table S4 in the supplementary material online). Therefore, it is unlikely that those patients obtained benefit from receiving a short protocol as ovary stimulation.

Several possible effects of GnRH agonist on ART outcomes have been proposed. The major hypothesis is that decapeptyl may facilitate development of the implanting embryo, work on the corpus luteum, and have a stimulatory effect on LH activity. In 1999, Raga et al[23] showed that peri-implantation of mouse embryos expressed GnRH receptor messenger RNA. Their *in vitro* development was significantly enhanced by incubation with a GnRH agonist and suppressed by incubation with increasing concentration of GnRH antagonist. Murdoch[24] and Reshef et al[25] also demonstrated the presence of the GnRH receptor in peri-implantation of human embryos and endometrial stromal cells in subsequent studies. Furthermore, Tesarik et al[4] demonstrated that administration of 0.1 mg triptorelin had a direct effect on early embryo development, as shown by a higher level of β-hCG. It is possible that midluteal administration of a GnRH agonist as luteal support may stimulate the secretion of hCG by early implantation of embryos. In other studies, a GnRH receptor was found to be immunolocalized in murine endometrium and a functional receptor was detected in the human uterus,[26,27] suggesting an effect on the regulation of embryo-endometrial interactions.

Second, in 2006 Pirard et al[28] hypothesized that GnRH agonist supports the corpus luteum by stimulation of LH either by pituitary gonadotroph cells or by acting on the GnRH receptor of the endometrium. The LH-releasing property of GnRH agonists not only supports the corpus luteum but also promotes the expression and secretion of relaxin by the corpus

luteum.[29] Furthermore, LH release had a positive effect on the endometrium, including stimulation of angiogenic growth factors and cytokines involved in implantation.[30−33] By maintaining the LH activity, GnRH agonist provide beneficial luteal support.

Decapeptyl as LPS may enhance the chance of OHSS, which may be cause for concern. As we can see, this was not observed in the decapeptyl group (Table 2).

In conclusion, administration of a GnRH agonist during the luteal phase is an optional treatment with potential benefits to the patients. We found that the GnRH agonist decapeptyl is effective in patients undergoing ICSI as an additional luteal support at least when a short protocol was used. The mechanisms involved probably act on the level of embryo implantation and the corpus luteum.

In addition to the use of a single administration of decapeptyl,[34−36] some authors reported beneficial outcomes with multiple administrations of luteal phase GnRH agonists.[28,37,38] Further optimization of the timing, dosage, and usage duration of GnRH agonists is warranted.

In our series, subgroups according to basal FSH > 8 mIU/mL or three or fewer mature oocytes in patients aged ≤38 years and no more than two previous cycles had significantly better pregnancy outcomes. The patients with no more than three mature oocytes may benefit from LPS with decapeptyl irrespective of stimulation protocol (see Table S4 in the supplementary material online). However, for another group of patients in the same hospital who were elderly and had more previous cycles as outlined in Tables S2 and S3 in the supplementary material online, decapeptyl did not offer better results. In 2007, Metallinou et al[39] suggested that GnRH agonist may directly inhibit progesterone production in human granulosa luteal cells and increase the number of apoptotic granulosa luteal cells, which are associated with unfavorable outcomes.[39] According to our results and current evidence, it is possible that LPS with decapeptyl may not be suitable for every patient. As such, we do not recommend routine use of GnRH agonist as LPS. Appropriate guidelines may be helpful in this situation. Unfortunately, there is currently no clear guideline regarding when to use decapeptyl as LPS. Because of the limitations inherent in a retrospective study and relatively small number of those subgroups, these supplemental analyses should be interpreted carefully and not be overinterpreted. Additional large-scale randomized controlled trials in this regard and subsequent development of a guideline is warranted.

Appendix 1. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcma.2014.07.001.

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