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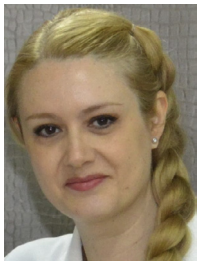
ARTICLE

GnRH agonist treatment of luteal phase deficiency in HCG-triggered IVF cycles: a matched case-control study



BIOGRAPHY

Raquel Mendoza-Tesarik graduated in Biological Science from Granada University in 2002. She has co-authored important research articles in the field of assisted reproduction. She is responsible for the Assisted Reproduction Laboratory at MAR&Gen Clinic in Granada.

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KEY MESSAGE

This matched case-controlled study shows that IVF failure associated with low serum progesterone levels after embryo transfer can be successfully treated by supporting the luteal phase with gonadotrophin releasing hormone agonist.

ABSTRACT

Research question: This study aimed to identify women with IVF failure associated with low serum progesterone levels after embryo transfer in HCG-triggered cycles and to evaluate the effects of gonadotrophin-releasing hormone (GnRH) agonist, administered after embryo transfer, on serum progesterone and pregnancy outcomes in these cases.

Design: Fifty women who failed to achieve an ongoing clinical pregnancy and had abnormally low luteal-phase serum progesterone concentrations in their first IVF attempt were assigned to two matched groups in their subsequent attempt. Twenty-five women were treated with the original protocol plus14 daily injections of GnRH agonist, beginning on the day of oocyte recovery, in their second IVF attempt (group 1). These women were matched to 25 women with the same characteristics and outcomes in their first IVF attempt who underwent the second IVF attempt without the use of GnRH agonist after embryo transfer (group 2). In both groups, the two sequential attempts were compared for serum progesterone concentration 14 days after oocyte recovery and pregnancy outcome.

Results: The patients in group 1 had significantly higher progesterone levels 14 days after oocyte recovery in the second attempt compared with the first attempt ($P < 0.001$), and 12 (48%) of them achieved clinical pregnancy and birth. No significant differences in pregnancy outcome or in the serum progesterone concentration were observed between the first and the second attempt in group 2.

Conclusions: In patients with luteal phase deficiency, the administration of GnRH agonist after embryo transfer increases serum progesterone concentration and improves the chance of pregnancy and birth.

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KEYWORDS
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INTRODUCTION

Luteal phase deficiency (LPD) is caused by impaired corpus luteum function resulting in abnormal oestradiol and progesterone production and shortening of the luteal phase, which has been implicated in the cause of irregular menstrual bleeding (*Fritz, 2012; Pfeifer et al., 2012*), infertility and early pregnancy loss (*Ginsburg, 1992*). The criteria to be used for the diagnosis of LPD is still a matter of debate. Use of low luteal phase serum progesterone as a diagnostic tool for LPD is plagued by the pulsatile release of progesterone from the corpus luteum, echoing the pulsatile release of LH from the pituitary (*Filicori et al., 1984*). A single serum progesterone level below 10 ng/ml (31.8 nmol/ml), however, measured in the mid-luteal phase, is considered as a relatively reliable indicator of LPD (*Jordan et al., 1994*); it has been suggested in a recent study (*Alsbjerg et al., 2018*) that the optimal cut-off of serum progesterone concentration for ongoing pregnancy, measured on pregnancy test day in cryopreserved embryo transfer cycles, should be 35 nmol/l (11 ng/ml). In our experience with fresh IVF treatment cycles (unpublished), however, serum progesterone levels less than 15 ng/ml (47.7 nmol/l), measured on the day of pregnancy test, are associated with reduced pregnancy rates. Therefore, 15 ng/ml was chosen as cut-off for the definition of LPD in this study.

Infertility treatments using IVF increase the risk of LPD, despite the development of multiple preovulatory follicles (*Garcia et al., 1981*). Therefore, various regimens of luteal phase support have been widely used in IVF, using HCG, oestradiol or progesterone administration during some time after embryo transfer (*Fatemi et al., 2007; Van der Linden et al., 2011*).

The beneficial effect of gonadotrophin releasing hormone (GnRH) agonist on human embryo implantation was first demonstrated by *Tesarik et al. (2004)*. As the luteal phase GnRH agonist administration was carried out in women receiving embryos from donated oocytes, in whom ovulation had been previously blocked, it was concluded that GnRH agonist exerted a direct effect on the implanting embryos (*Tesarik et al., 2004*). Further studies, however, showed a similar beneficial effect of luteal GnRH agonist in ovulating women, in both GnRH agonist- and antagonist-controlled ovarian stimulation cycles (*Tesarik et al., 2006; Pirard et al., 2015*), suggesting that GnRH agonist may also affect the corpus luteum function. This assumption was further corroborated by the observation that GnRH agonist can rescue the corpus luteum function in GnRH antagonist-controlled and GnRH-agonist triggered ovarian stimulation cycles (*Bar-Hava et al., 2016*). These protocols of ovarian stimulation, mostly used in women at a high risk of ovarian hyperstimulation syndrome, are known to result in a luteolytic effect that significantly lowers pregnancy rates (*Leth-Moller et al., 2014*).

On the basis of the above observations, it has been hypothesized that luteal phase support with GnRH agonist may be of help to all women, treated by assisted reproduction, who show low serum progesterone levels in the luteal phase, and even in those with corpus luteum deficiency in natural conception cycles (*Tesarik et al., 2016*). In our IVF programme, determination of serum progesterone concentration is made in all women on the day of embryo transfer and 14 days after oocyte recovery, together with the first beta-HCG test. Some patients who fail to achieve an ongoing pregnancy show abnormally low progesterone levels at this time.

The present study reports on 50 women falling into this category. Individual women were prospectively assigned to two matched groups, according to their age, body mass index and ovarian reserve. They were informed about the treatment received and signed a corresponding consent form. In group 1, after the first attempt with standard luteal phase support with vaginally administered progesterone, a second attempt was carried out with a combination of vaginal progesterone and daily subcutaneous GnRH agonist injections during the 2 weeks after oocyte recovery. In group II, the second attempt was carried out exactly as the first one, without the use of GnRH agonist after embryo transfer. Pregnancy outcome and serum progesterone concentration in the two sequential attempts were compared on day 14 after oocyte recovery.

MATERIALS AND METHODS

Study design and participants

This prospective matched case-control study included data from the medical records of 50 women aged between 25 and 40 years, entering the IVF programme of MARGen Clinic, Granada Spain, between January 2015 and April 2018. All of them failed to achieve an ongoing clinical pregnancy in their first IVF attempt and showed low serum progesterone concentrations (<15 ng/ml) on day 14 after oocyte recovery despite luteal phase support with vaginally administered micronized progesterone (600 mg daily), beginning on the day of oocyte recovery. This study only includes treatment cycles with fresh ejaculated spermatozoa and fresh embryos transferred on day 3 after oocyte recovery. Cycles with cryopreserved spermatozoa and those with blastocyst transfer were excluded. In fact, most embryo transfers are carried out on day 3 at our centre, based on previously published observations that day-3 embryo transfer with combined evaluation at the pronuclear and cleavage stages compares favourably with day-5 blastocyst transfer (*Rienzi et al., 2002*). Other exclusion criteria were andrological, gynaecological and systemic pathologies, including azoospermia, necrozoospermia, uterine polyps and fibroids, polycystic ovary syndrome, endometriosis, adenomyosis, Cushing syndrome, diabetes, hypothyreosis and hyperthyreosis, and body mass index higher than 29). Male factor was the main indication for IVF; therefore, IVF was carried out by intracytoplasmic sperm injection (ICSI) in all cases.

The women included in this study were assigned to two groups, matched for age, body mass index, basal antral follicle count and serum anti-Müllerian hormone concentrations. In group 1 (25 women), a second IVF attempt was carried out with the same ovarian stimulation protocol and laboratory techniques as the first one, but included daily injections of 0.1 mg triptorelin (Decapeptyl, Ipsen Pharma), administered in the evening over the 14 days beginning on the day of oocyte retrieval. The same regimen of vaginal progesterone administration (600 mg daily, divided in three 200 mg doses, in the morning, at noon and in the evening) was used in both the first and the second attempt. The second IVF attempt (with luteal phase agonist) was carried out 2–5 months after the first one (without the agonist). Only these first two attempts, carried out in each patient, are included in this study. In group 2, both the first and the second IVF attempts were carried out

with the same luteal phase support, with vaginal progesterone administration only (without the use of GnRH agonist).

All procedures carried out in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. The study was approved by the Institutional Review Board of the MARGen Clinic and the University of Granada on September 1, 2016 (reference number 07-16-FMMT). Informed consent was obtained from all individual participants included in this study.

Primary and secondary outcome measures

The primary outcome measure was ongoing clinical pregnancy rate (number of ongoing pregnancies divided by the number of embryo transfer procedures). It was obtained from medical records 3 months after embryo transfer. Ongoing clinical pregnancy was defined as the presence of at least one fetal heart pulsation beyond 20 weeks.

Serum progesterone concentration, measured using immunoassay on day 14 after embryo transfer, was used as a secondary outcome measure. The blood samples for progesterone concentration measurements were taken early in the morning, before the first progesterone administration of the day.

Assisted reproduction techniques and embryo evaluation

Intracytoplasmic sperm injection was used for all IVF procedures after ovarian stimulation using a combination of recombinant human FSH (Puregon, Merck Sharp & Dohme), human menopausal gonadotrophin (Menopur, Ferring Pharmaceuticals) and GnRH antagonist (Orgalutran, Merck Sharp & Dohme). Details of the ICSI technique (*Tesarik et al., 2002*) and the ovarian stimulation protocol (*Tesarik and Mendoza, 2002; Altmäe et al., 2018*) used in this study have been described previously. The same protocols were used in the first and second treatment attempt. In all cases, ovulation was induced with 250 µg recombinant human HCG (Ovitrelle, Merck) 36.5 h before ultrasound-guided ovarian puncture for oocyte retrieval. Uterine transfer of one to three embryos was carried out under ultrasound guidance on day 3 after oocyte recovery. The quality of embryos was assessed by combining the evaluation of pronuclear stage zygotes (*Tesarik and Greco, 1999*) and cleaving embryos on the days 2 and 3 after ICSI as described (*Rienzi et al., 2002*). The embryos with the highest cumulative scores from these evaluations (*Rienzi et al., 2002*) are referred to as top embryos.

Statistical analysis

Continuous variables were presented as means ± SD and compared by Mann–Whitney U-test or Wilcoxon's matched pairs rank sum test. Proportional values were compared by Pearson chi-squared or McNemar chi-squared analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Group 1

Basic characteristics of the two successive IVF attempts

The two successive IVF attempts did not differ in either total number of oocytes recovered or the number of metaphase II oocytes that were treated by ICSI (TABLE 1). The biological outcomes of both the first and the second IVF attempt, in terms of the number of normal two-pronucleated zygotes, total cleaving embryos and those considered of top quality, were also the same in both attempts (TABLE 1).

Effect of luteal phase GnRH agonist administration on serum progesterone concentration

As shown in TABLE 2, serum progesterone concentration, measured on the day of embryo transfer, was not significantly different in the second attempts, using the luteal phase support with GnRH agonist, compared with the first attempts, which did not include luteal GnRH agonist administration. In contrast, the progesterone concentration on day 14 after oocyte retrieval was around three times higher ($P < 0.001$) in the attempts using luteal phase GnRH agonist administration compared with those without the agonist (TABLE 2). The difference between the progesterone concentration on day 14 after oocyte recovery between the GnRH agonist group and the standard treatment group was significant both in the patients who became pregnant ($P < 0.002$) and those who did not ($P < 0.007$) (TABLE 3), although the difference was more pronounced in the pregnant patient group. This suggests that the implanting embryo itself marginally contributed to the corpus luteum stimulation, in addition to the exogenous GnRH agonist.

Effect of luteal phase GnRH agonist administration on IVF outcomes

Despite the same number (TABLE 4) and quality (TABLE 1) of the embryos transferred per patient in the two

TABLE 1 COMPARISON OF OOCYTE YIELD, FERTILIZATION AND EMBRYO DEVELOPMENT IN TWO SUCCESSIVE ATTEMPTS WITHOUT AND WITH GONADOTROPHIN RELEASING HORMONE AGONIST TREATMENT, CARRIED OUT IN 25 PATIENTS

GnRH agonist	*Not used*	*Used*
Total oocytes	9.8 ± 3.7	10.0 ± 3.7
Oocytes injected	8.2 ± 2.9	8.5 ± 2.9
Normal zygotes	6.9 ± 2.2	7.0 ± 2.5
Total embryos	6.4 ± 2.0	6.6 ± 2.1
Top embryos	4.0 ± 1.2	4.2 ± 1.2

Values are presented as mean ± SD. No statistically significant differences were found between the two groups.

GnRH, gonadotrophin releasing hormone.

TABLE 2 COMPARISON OF LUTEAL PHASE CHARACTERISTICS IN TWO SUCCESSIVE ATTEMPTS WITHOUT AND WITH GONADOTROPHIN RELEASING HORMONE AGONIST TREATMENT, CARRIED OUT IN 25 PATIENTS

GnRH agonist		*Not used*	*Used*	*P-value*
Serum progesterone (ng/ml)	Day of embryo transfer	11.5 ± 2.7	12.0 ± 2.4	NS
	Day 14 after embryo transfer	13.3 ± 1.9	38.2 ± 14.6	<0.001

Values are presented as mean ± SD.

GnRH, gonadotrophin releasing hormone; NS, not statistically significant.

TABLE 3 COMPARISON OF LUTEAL PHASE CHARACTERISTICS IN TWO SUCCESSIVE ATTEMPTS WITHOUT AND WITH GNRH AGONIST TREATMENT, CARRIED OUT IN PATIENTS WHO ACHIEVED AN ONGOING CLINICAL PREGNANCY WITH GNRH AGONIST AND THOSE WHO DID NOT

GnRH agonist		*Not used*	*Used*	*P-value*
Serum progesterone on day 14 after embryo transfer (ng/ml)	Pregnant patients (n = 12)	14.0 ± 1.8	45.4 ± 12.0	<0.002
	Non-pregnant patients (n = 10)	12.4 ± 1.6	25.9 ± 7.7	<0.007

The three patients who became pregnant in both attempts are not included.

Values are presented as mean ± SD.

TABLE 4 COMPARISON OF PREGNANCY AND ONGOING CLINICAL PREGNANCY RATES IN TWO SUCCESSIVE ATTEMPTS WITHOUT AND WITH GNRH AGONIST TREATMENT, CARRIED OUT IN 25 PATIENTS

GnRH agonist		*Not used*	*Used*	*P-value*
Embryos transferred per attempt, mean ± SD		2.1 ± 0.5	2.2 ± 0.4	NS
Pregnancies, n (%)	Positive beta-HCG	3 (12)	15 (60)	<0.001
	Clinical ongoing	0 (0)	12 (48)	<0.001

NS, not statistically significant.

successive attempts, both the pregnancy rate (60% versus 12%) and the clinical pregnancy rate (48% versus 0%) were significantly higher (both $P < 0.001$) in the attempts using the luteal phase support with GnRH agonist compared with those without the agonist (TABLE 4). All of the clinical pregnancies resulted in the birth of normal babies.

Group 2

As with Group 1, the two successive IVF attempts did not differ in the total number of oocytes recovered, the number of metaphase II oocytes that were treated by ICSI, the number of normal two-pronucleated zygotes, total cleaving embryos and top-quality embryos (data not shown). Moreover, both the first and the second attempt resulted in similar serum progesterone concentrations measured on the day of embryo transfer (11.2 ± 2.5 versus 11.6 ± 2.8 ng/ml) and on day 14 after oocyte recovery (12.3 ± 2.6 versus 12.6 ± 2.0 ng/ml).

With similar numbers of embryos transferred in the first and second attempt (2.0 ± 0.5 versus 2.3 ± 0.6), pregnancy (as detected by positive beta-HCG test) was established in two (8%) and three (12%) cases, respectively. Both pregnancies established in the first attempt were lost before detecting embryonic heartbeat. One of the three pregnancies, however, established in the second attempt was ongoing and resulted in the birth of a healthy child. None of the above differences between the first and the second attempt in group 2 of women was statistically significant.

DISCUSSION

Luteal phase deficiency, in terms of insufficient secretion of progesterone by the corpus luteum, reflected by low serum progesterone levels, can occur in IVF attempts using any kind of ovarian stimulation protocol (*Garcia et al, 1981; Fatemi et al, 2007; Van den Linden et al., 2011*). It is particularly frequent, however, in ovarian stimulation cycles controlled by GnRH antagonist in which GnRH agonist is used as ovulation trigger (*Leth-Moller et al., 2014; Bar-Hava et al., 2016*). *Bar-Hava et al. (2016)* have shown recently that daily administration of GnRH agonist during the early luteal phase of IVF cycles using GnRH agonist, instead of HCG, for ovulation induction rescues corpus luteum function and is also sufficient to support embryo implantation and further development without the need of any other kind of luteal phase support therapy. In the present study, we used a similar approach in a particular group of patients, characterized by LPD occurring even after IVF using recombinant HCG to trigger ovulation. These data show that LPD can occur in some patients independently of the type of ovulation trigger used, and that this problem can also be resolved by prolonged luteal phase administration of GnRH agonist.

Unlike the study by *Bar-Hava et al. (2016)*, luteal phase of patients involved in the present study was not supported uniquely by GnRH agonist, but vaginal progesterone administration was also used. This choice was motivated by ethical reasons, as it was not clear whether GnRH agonist would function, with this particular group of patients and ovarian stimulation protocol, in a similar way as in the study by *Bar-Hava et al. (2016)*. This could not compromise the data interpretation, however, because the same doses of progesterone were administered in all treatment cycles, both those using luteal phase GnRH agonist administration and those without the agonist. Because of the self-control design of this study, there is no reason to suppose that the basal level of serum progesterone, resulting from external progesterone administration, were significantly different in the two successive attempts carried out in the same patients.

For the patients who received GnRH agonist in the second cycle, the values of serum progesterone were similar in both attempts on the day of embryo transfer, but they were significantly different on day 14 after oocyte recovery. This suggests that the early corpus luteum (the first 3 days after oocyte retrieval) are not yet responsive to GnRH agonist action, and the serum progesterone measured was basically a result of external progesterone administration. Alternatively, a longer exposure to GnRH agonist may be needed to enhance corpus luteum progesterone secretion. The mid-luteal progesterone levels, however, were significantly higher in the GnRH agonist-treated cycles even in those patients who did not become pregnant after this treatment, although the values of the pregnant patients were

higher than those of the non-pregnant ones. This can be explained by an effect of the pregnancy itself on the corpus luteum progesterone secretion (*Takaya et al., 2018*), in addition to that of GnRH agonist. Therefore, the consistently higher progesterone levels in the successful and unsuccessful cycles treated with luteal phase GnRH agonist compared with the untreated cycles clearly show that GnRH agonist increased the patients' own progesterone production, despite administration of the same dose of external progesterone. This increase was accompanied by a significant improvement of pregnancy outcomes in the GnRH agonist-treated IVF cycles, whereas other cycle characteristics, which could theoretically affect success rates, were comparable in both the GnRH agonist-treated and the untreated attempts.

Although the present data clearly show that luteal administration of GnRH agonist stimulates the production of progesterone by the corpus luteum in women with LPD, the mechanism of this action is not clear. In addition to its effect on the corpus luteum, GnRH agonists seem to target some other processes related to embryo implantation. It has to be reminded that the first report on a beneficial effect of GnRH agonist administration after embryo transfer was based on data obtained in egg donation cycles, after previous suppression of the recipients' ovarian activity, a condition leading to a complete absence of the corpus luteum (*Tesarik et al., 2004*), thus excluding any action of GnRH agonists at this level. It was concluded that GnRH agonists acted through an enhancement of embryo developmental potential (*Tesarik et al., 2004*). Later studies, however, have shown that GnRH agonists also improved IVF/ICSI outcomes after ovarian stimulation (*Tesarik et al., 2006; Pirard et al., 2015*), thus adding the corpus luteum as another possible target, and this idea has been further corroborated by the finding that continuous GnRH agonist after embryo transfer can completely substitute for exogenous progesterone in GnRH antagonist-controlled and GnRH agonist-triggered ovarian stimulation regimens (*Bar-Hava et al., 2016*).

Moreover, there is a third possible GnRH agonist target – the endometrium. The human endometrium has been shown to express high levels of both GnRH and GnRH receptors (*Maggi et al., 2016*), and GnRH agonists affect the function of the urokinase-type plasminogen activator/plasminogen activator inhibitor system in human decidual stromal cells (*Chou et al., 2003*) and regulate the motility of human decidual endometrial stromal cells (*Wu et al., 2015*).

It remains to be evaluated whether, and to what extent, LPD can contribute to unexplained infertility in natural conception cycles. If this hypothesis is confirmed, GnRH agonist treatment during the luteal phase can be used in selected cases of unexplained infertility without the need for IVF.

In conclusion, the present study shows that, first, LPD can be associated with otherwise unexplained IVF failure and, second, daily administration of GnRH agonist during 2 weeks after oocyte recovery can resolve this problem.

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