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ARTICLE

Luteal phase support post IVF: individualized early stop

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Abstract While the need for progesterone-based luteal phase support is well documented, the required treatment duration is not well established, and a practitioners' survey showed a wide range of empiric stopping points. It is suggested that an early stop can be based on assessing endogenous luteal activity on the day of pregnancy test. To examine this approach, data were retrospectively collected on 99 patients with positive pregnancy test and high serum concentrations of oestradiol and progesterone (≥1000 pmol/l and ≥110 nmol/l, respectively), whose luteal support was stopped, and compared with those of 85 patients who did not meet the above criteria, and so luteal support was continued until gestational week 9. Both groups were comparable in terms of live birth and miscarriage rates. We conclude that in the face of strong endogenous luteal activity, exogenous support can be stopped on pregnancy test day, without affecting pregnancy outcome. Further research is needed to substantiate this finding.

KEYWORDS: early pregnancy, individualized treatment, luteal phase support, oestradiol, ovarian stimulation, progesterone

Introduction

Progesterone-based luteal phase support (LPS) is routinely recommended in all assisted reproductive technology (ART) cycles (The Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society for Reproductive Endocrinology and Infertility, 2008; Van der Linden et al., 2011). Ovarian stimulation with gonadotrophins, gonadotrophin-releasing hormone (GnRH) analogues to block premature ovulation and the use of human chorionic gonadotrophin (HCG) to trigger ovulation lead to corpora lutea overstimulation during the early luteal phase, resulting in supra-physiologic oestradiol and progesterone concentrations. These, in turn, suppress pituitary LH secretion (Andersen and Andersen, 2014; Fatemi et al., 2007). In mid- to late-luteal phase, decreasing exogenous HCG concentrations may

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not coincide with increasing endogenous HCG secretion from implanting embryo(s), which together with the considerable mid-luteal reduction in LH-like activity, result in a crucial window of luteal phase defect (Andersen and Andersen, 2014). The main purpose of luteal phase support is to bridge this potential fall in endometrial progresterone (and oestradiol) exposure.

While the need for LPS is well documented, the timeframe for its use is a matter of debate. In a retrospective study covering 400 patients treated with GnRH agonist, Schmidt et al. (2001) showed that an early (14 days post-embryo transfer) stop in 200 patients resulted in good clinical outcome (delivery rate) compared with 200 patients who stopped LPS 3 weeks later. In a following randomized controlled trial (RCT) involving 303 patients, Andersen et al. (2002) confirmed the above result. Similarly, Kyrou et al. (2011) confirmed that early progesterone cessation has no influence on pregnancy outcome in GnRH antagonist cycles either. However, in a recent survey covering 284,600 patients in 408 ART centres, Vaisbuch et al. (2012) reported that in 72% of the cycles LPS were administered until 8–10 weeks' gestation or beyond. Only in 15% of the cycles, LPS was administered until pregnancy was confirmed by a positive pregnancy test and discontinued thereafter. Surveying 21 leading IVF centres, Aboulghar et al. (2008) confirmed that there is no international consensus about the duration of LPS. Looking at the available literature there is a lack of evidence-based recommendation on when to stop LPS (Miles et al., 1994; Schoolcraft et al., 2000; Smitz et al., 1992; Van Steirteghem et al., 1998). It may be concluded, unfortunately, that bewildered practitioners and puzzled patients (fully exposed to web-based conflicting information) team up for a completely empiric approach to this question. One may argue, therefore, that the both practitioners and patients need a patient-specific confirmatory evidence that LPS can be safely withdrawn without jeopardizing the pregnancy.

In the above-mentioned survey, Vaisbuch et al. (2012) also reported that the vast majority of practitioners (77%) use only vaginal progesterone preparation for LPS. Patient comfort should be a concern here, since leaky and messy vaginal progesterone preparations are not met with great enthusiasm by patients, unless deemed completely necessary. In addition, there is still some concern for potential progesterone teratogenic effect, since its prenatal use has been related to competitively inhibiting the conversion of testosterone to dihydrotestosterone (Carmichael et al., 2005; Silver, 2004). Taken together, LPS early cessation is of significant advantage; however, an individualized approach is mandatory to make such a decision, if an empirical approach is to be avoided.

In a prospective study covering 442 patients treated by IVF or intracytoplasmic sperm injection (ICSI), Ioannidis et al. (2005) demonstrated that a single serum progesterone measurement on day 14 post-oocyte retrieval could highly differentiate between normal and abnormal pregnancies, and therefore be a useful indicator of pregnancy outcome. The main corpus luteum steroidogenesis activity is manifested in oestradiol and progesterone secretion. Therefore, their measurement on pregnancy test day may reflect individual luteal activity. As concluded by Ioannidis et al. (2005), high concentrations of serum progesterone suggest that endogenous progesterone is already sufficient in a viable pregnancy. Therefore we suggest that if both oestradiol and progesterone (measured 14 days post-oocyte retrieval) are above threshold concentrations, LPS can be safely stopped. This strategy was implemented in our centre, and the purpose of this publication is to report our experience, invoking further RCT in this direction.

The main purpose of the present study is to examine retrospectively the outcome of pregnancies during which LPS was terminated 14 days post-oocyte retrieval using oestradiol and progesterone measurements to ascertain robust endogenous luteal activity.

Materials and methods

Data on 184 IVF or ICSI cycles performed at the IVF Unit, Rambam Health Care Campus between the years 2005 and 2014 were obtained from 180 patient files. All cycles preformed at the unit that met the inclusion criteria were included in this study.

Inclusion criteria

- Patients with positive β-HCG test 14 days post-oocyte retrieval, with concomitant measurement of oestradiol and progesterone.
- LPS by progesterone-only medication (vaginal or intramuscular).
- A clinical viable pregnancy demonstrated by a transvaginal ultrasound 1 month post-oocyte retrieval.
- Complete follow-up of pregnancy and delivery or miscarriage, after a viable pregnancy was ascertained.

Exclusion criteria

- Patients with missing data on progesterone and or oestradiol concentrations 14 days post-oocyte retrieval.
- Missing data on cessation or continuation of LPS as many patients continue pregnancy follow-up in community services.
- Patients who received HCG for LPS.

Protocol

Ovarian stimulation was performed with either the GnRH agonist 'long' or GnRH antagonist 'short' protocols. Cycles were monitored according to the policy of the clinic. Recombinant HCG (Ovitrelle 250 μg, Serono) was administered as soon as three leading follicles reached ≥17 mm mean diameter; oocyte retrieval was performed 34–36 h later. Oocytes were fertilized with conventional IVF or ICSI, according to individual patient criteria. LPS was started the on the day of embryo transfer (2–3 days post-oocyte retrieval) by a progesterone-only preparation. The primary outcome of the study was live birth.

Hormonal measurement and criteria for LPS cessation

Serum β-HCG, progesterone and oestradiol concentrations were measured 14 days post-oocyte retrieval. If β-HCG were positive, the criteria for immediate LPS stop were:

- oestradiol level ≥ 1000 pmol/l
- progesterone ≥ 110 nmol/l.

Otherwise, LPS was continued to gestational week 9.

Pregnancy follow-up

β-HCG measurement was repeated within the first 7 days after the first one, to rule out biochemical pregnancy. Viable pregnancy was ascertained by transvaginal sonography 1 month post-oocyte retrieval, and the number of embryos with normal fetal heart activity was recorded. Pregnancy outcome was recorded from the Rambam Health Care campus database, or by a phone call if the patient delivered in another hospital.

The study was approved by the Rambam Health Care campus Institutional Review Board on 9 June 2015 (reference number 0060-15-RMB).

Statistical analysis

The association of LPS variants (continue, stop) and outcome (live birth, miscarriage) was examined using a Pearson chi-squared test. The comparisons of LPS groups and other continuous data were done using independent samples *t*-test, and the comparisons of LPS groups and other categorical data were done using Pearson chi-squared and Fisher's exact tests.

Significance was set at $P < 0.05$ for all tests.

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS version 20.0.0.0, IBM Corp., USA).

Results

In total, 184 IVF or ICSI cycles were included. In 99 cycles LPS was stopped 14 days post-oocyte retrieval, and in 85 cycles LPS was continued based on hormonal measurements and criteria for LPS cessation.

Baseline characteristics (age, aetiology of infertility, fertilization procedure, protocol, number of oocytes retrieved, number of embryos obtained and transferred, type of LPS given), were similar between the two groups (Table 1).

Live birth rate was comparable between the two groups with 92.9% and 87.2% in the stop and continue groups, respectively (Table 2). Miscarriage rate was similar between the two groups: 7.1% and 12.8% in the stop and continue groups, respectively. These miscarriage rates are comparable with those described previously (Andersen et al., 2002; Kohls et al., 2012; Schmidt et al., 2001).

Day 14 post-oocyte retrieval serum β-HCG, progesterone and oestradiol concentrations were significantly different between the two groups, with the concentrations of all three significantly higher in the LPS stop group (all $P < 0.001$, Table 2).

Table 1 Baseline characteristics of the groups with LPS continuation or cessation.

	Continuation of LPS (n = 85)	*Cessation of LPS (n = 99)*
Age (years)	30.5 ± 5.3	30.8 ± 5.4
Aetiology of infertility (%)[a]		
Male factor	63.8	58.3
Female factor	9.6	13.1
Unexplained	14.9	15.5
Combined	11.7	13.1
Fertilization procedure (%)		
ICSI	68.2	75.8
IVF	27.1	21.2
Combined	4.7	3.0
Protocol (%)		
Long	24.7	22.2
Short	75.3	77.8
Number of oocytes retrieved	10.7 ± 5.7	11.2 ± 5.7
Number of fertilized oocytes[b]	6.5 ± 4.0	7.0 ± 3.9
Number of embryos obtained	5.9 ± 3.7	5.9 ± 3.4
Number of embryos transferred	2.4 ± 0.7	2.2 ± 0.7
Type of progesterone supplementation (%)		
Vaginal	96.5	100
Intramuscular	3.5	0

There were no statistically significant differences between the two groups.
[a]Data were missing in six files.
[b]Data were missing in nine files.
ICSI = intracytoplasmic sperm injection; LPS = luteal phase support.

Discussion

To our knowledge, this is the first study to introduce the concept of individualized early LPS stop based on oestradiol and progesterone serum concentrations on the day of pregnancy test post-IVF. The present results suggest that these measurements can be used to individually assess whether continuous LPS is required. If both hormones reflect robust endogenous luteal activity, any additional progesterone is redundant, so LPS can be safely stopped without any fear of negative effect on pregnancy outcome.

Corpora lutea function after ovarian stimulation, HCG trigger and oocyte retrieval may be defective in steroid secretion, but may be rescued by endogenous HCG production by the newly formed placenta. It is difficult to predict if this rescue occurs in advance, because of the interaction of multiple variables: degree of ovarian stimulation, pituitary down-regulation in GnRH agonist 'long' protocols (especially if a long-acting preparation is used), clearance dynamics of HCG bolus used for trigger, degree of pituitary suppression during early luteal phase and timing (and accelerated secretion pattern) of endogenous HCG produced by the newly formed placenta, to name the most important ones. However, we suggest that all these variables culminate to a simple, low-cost test

Table 2 Hormone concentrations as measured 14 days post-oocyte retrieval in the groups with LPS continuation or cessation.

	Continuation of LPS (n = 85)	*Cessation of LPS (n = 99)*	*P-value*
HCG concentrations on 14th day post-oocyte retrieval (IU/l)	106.1 ± 83.1	216.9 ± 205.2	<0.001
Progesterone concentrations on 14th day post-oocyte retrieval (nmol/l)	47.3 ± 24.8	172.7 ± 69.9	<0.001
Oestradiol concentrations on 14th day post oocyte retrieval (pmol/l)	984.6 ± 675.7	4651.9 ± 2779.8	<0.001
Number of gestational sacs[a] (%)			NS
1	79.8	73.2	
2	20.2	24.7	
3	0	2.1	
Pregnancy outcome (%)			NS
Live birth	87.1	92.9	
Miscarriage	12.9	7.1	
Number of newborn(s) (%)			NS
1	85.1	78.3	
2	14.9	20.6	
3	0	1.1	

[a]Data were missing in three files.
HCG = human chorionic gonadotrophin; LPS = luteal phase support; NS = not statistically significant.

(oestradiol and progesterone serum concentrations) that can confirm luteal phase rescue. Therefore, the clinician can base the decision of LPS cessation on objective, patient-specific variables. These clear criteria may also contribute to patients' confidence, being bombarded by web-based conflicting information, that indeed continued LPS is redundant, and its early stop will not jeopardize precious pregnancies.

Interestingly, initial high β-HCG concentration is associated with healthy luteal function. It may reflect an early appearance of endogenous HCG secretion, or a more rapid increase in placental-derived HCG production. Either way, it helps to bridge the time gap between exogenous (used for trigger) and endogenous HCG appearance, associated with corpora lutea rescue.

It may be argued that progesterone serum concentrations fluctuate significantly in a pulsatile manner (described by Nakajima et al., 1990) and therefore cannot be taken to reflect luteal activity. We maintain that in a multi corpora lutea situation a simultaneous pulse frequency is highly improbable. Moreover, the accompanied high oestradiol concentration, as a secondary criterion in this study (no exogenous oestradiol was given), further reassures us that indeed endogenous luteal activity is more than sufficient to maintain pregnancy. It is assumed that progesterone concentrations of >30 nmol/l may be sufficient to maintain pregnancy (Kohls et al., 2012). Yovich et al. (1985) found that in IVF cycles, luteal phase data indicated that progesterone concentrations were two to three times higher than that expected during spontaneous conception cycles and those pregnancies that subsequently aborted had significantly lower concentrations in the late luteal phase. Therefore, we suggest that setting a threshold concentration at ≥110 nmol/l leaves us with a very wide safety margin.

Vaginal progesterone preparations are also used in programmed (no endogenous luteal activity) thaw cycles, to induce timely endometrial luteal shift. Most IVF centres follow these patients with progesterone serum measurements to ascertain compliance and absorption, so each programme can formulate the average serum progesterone concentration measured in these cycles. Translating into 'fresh' cycles, this average may delineate the exogenous progesterone contribution to the progesterone serum concentration measured on pregnancy test day, and therefore, give a good estimate of the endogenous progesterone production, directly reflecting corpora lutea activity.

Why is an early stop of redundant LPS important?

In the era of evidence-based medicine, and individualized approach to treatment, empirical use of such a prolonged treatment seems inappropriate and must be discouraged. A great emphasis has been put on an individualized approach to ovarian stimulation (for example: Fiedler and Ezcurra, 2012); however, not much attention has been devoted to the luteal phase in that context.

As mentioned above, exogenous progesterone supplementation during early pregnancy has been associated with the risk of minor birth defects, although the evidence is not very strong (Carmichael et al., 2005; Silver, 2004).

Progesterone supplementation is considered to be harmless, but is a source of complaint by patients, whether because of continuous vaginal messy leakage from vaginal formulations, or painful intramuscular injections. Patient comfort must be an important consideration in the field of ART. A great deal of research and development has been done to ease treatment burden during the follicular phase, the introduction of corifollitropin α being a bold example (Fauser et al., 2009). Unfortunately, such close attention and resources were never given to the much longer luteal phase (if pregnancy is achieved), where early LPS stop, as we suggest, may cut down on many weeks of redundant miserable treatment (not only six injections as in the case of corifollitropin α). This has two main implications: first, decreasing treatment burden and patient dropouts; and second, significant decrease in treatment cost.

There is a potential global effect: it is estimated that about 1 million IVF cycles are performed annually around the world. If early LPS stop policy is to be adopted, cost savings will be significant.

The obvious disadvantage of the present study is its retrospective nature. However, the two groups were similar in

most characteristics, including live birth rate. Thus, we propose that LPS can be safely withdrawn in the face of robust luteal activity. A randomized controlled study to substantiate these findings is warranted.

In summary, an individualized approach to treatment is a theme that must be implemented in the case of LPS treatment duration. We suggest a simple, low-cost way to assess patient-specific endogenous luteal activity, on which to reach an educated decision about the need to continue LPS beyond the pregnancy test day.

References

Aboulghar, M.A., Amin, Y.M., Al-Inany, H.G., Aboulghar, M.M., Mourad, L.M., Serour, G.I., Mansour, R.T., 2008. Prospective randomized study comparing luteal phase support for ICSI patients up to the first ultrasound compared with an additional three weeks. Hum. Reprod. 23, 857–862.

Andersen, A.N., Popovic-Todorovic, B., Schmidt, K.T., Loft, A., Lindhard, A., Hojgaard, A., Ziebe, S., Hald, F., Hauge, B., Toft, B., 2002. Progesterone supplementation during early gestations after IVF or ICSI has no effect on the delivery rates: a randomized controlled trial. Hum. Reprod. 17, 357–361.

Andersen, C.Y., Andersen, K.V., 2014. Improving the luteal phase after ovarian stimulation: reviewing new options. Reprod. Biomed. Online 28, 552–559.

Carmichael, S.L., Shaw, G.M., Laurent, C., Croughan, M.S., Olney, R.S., Lammer, E.J., 2005. Maternal progestin intake and risk of hypospadias. Arch. Pediatr. Adolesc. Med. 159, 957–962.

Fatemi, H.M., Popovic-Todorovic, B., Papanikolaou, E., Donoso, P., Devroey, P., 2007. An update of luteal phase support in stimulated IVF cycles. Hum. Reprod. Update 13, 581–590.

Fauser, B.C., Mannaerts, B.M., Devroey, P., Leader, A., Boime, I., Baird, D.T., 2009. Advances in recombinant DNA technology: corifollitropin alfa, a hybrid molecule with sustained follicle-stimulating activity and reduced injection frequency. Hum. Reprod. Update 15, 309–321.

Fiedler, K., Ezcurra, D., 2012. Predicting and preventing ovarian hyperstimulation syndrome (OHSS): the need for individualized not standardized treatment. Reprod. Biol. Endocrinol. 10, 32.

Ioannidis, G., Sacks, G., Reddy, N., Seyani, L., Margara, R., Lavery, S., Trew, G., 2005. Day 14 maternal serum progesterone levels predict pregnancy outcome in IVF/ICSI treatment cycles: a prospective study. Hum. Reprod. 20, 741–746.

Kohls, G., Ruiz, F., Martinez, M., Hauzman, E., de la Fuente, G., Pellicer, A., Garcia-Velasco, J.A., 2012. Early progesterone cessation after in vitro fertilization/intracytoplasmic sperm injection: a randomized, controlled trial. Fertil. Steril. 98, 858–862.

Kyrou, D., Fatemi, H.M., Zepiridis, L., Riva, A., Papanikolau, E.G., Tarlatzis, B., Devroey, P., 2011. Is cessation of progesterone supplementation during early pregnancy in patients treated with recFSH/GnRH antagonist noninferior to its continuation regarding pregnancy outcomes? A randomized controlled trial. Hum. Reprod. 26, 1020–1024.

Miles, R.A., Paulson, R.B., Lobo, R.A., Press, M.F., Dahmoush, L., Saner, M.V., 1994. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular or vaginal routes: a comparative study. Fertil. Steril. 62, 485–490.

Nakajima, S.T., McAuliffe, T., Gibson, M., 1990. The 24-hour pattern of the levels of serum progesterone and immunoreactive human chorionic gonadotropin in normal early pregnancy. J. Clin. Endocrinol. Metab. 71, 345–353.

Schmidt, K.L., Ziebe, S., Popovic, B., Lindhard, A., Loft, A., Andersen, A.N., 2001. Progesterone supplementation during early gestation after in vitro fertilization has no effect on the delivery rate. Fertil. Steril. 75, 337–341.

Schoolcraft, W.B., Hesla, J.S., Gee, M.J., 2000. Experience with progesterone gel for luteal support in a highly successful IVF programme. Hum. Reprod. 15, 1284–1288.

Silver, R.I., 2004. Endocrine abnormalities in boys with hypospadias. Adv. Exp. Med. Biol. 545, 45–72.

Smitz, J., Erard, P., Camus, M., Devroey, P., Tournaye, H., Wisanto, A., Van Steirteghem, A.C., 1992. Pituitary gonadotrophin secretory capacity during the luteal phase in superovulation using GnRH-agonists and HMG in a desensitization or flare-up protocol. Hum. Reprod. 7, 1225–1229.

The Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society for Reproductive Endocrinology and Infertility, 2008. Progesterone supplementation during the luteal phase and in early pregnancy in treatment of infertility: an educational bulletin. Fertil. Steril. 90, s150–s153.

Vaisbuch, E., Leong, M., Shoham, Z., 2012. Progesterone support in IVF: is evidencebased medicine translated to clinical practice? A worldwide web-based survey. Reprod. Biomed. Online 25, 139–145.

Van der Linden, M., Buckingham, K., Farquhar, C., Kremer, J.A., Metwally, M., 2011. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst. Rev. (10), CD009154.

Van Steirteghem, A., Smitz, J., Camus, M., Van Waesberghe, L., Descacht, J., Khan, I., Stuessen, C., Wisanto, A., Bourgain, C., Devroey, P., 1998. The luteal phase after in-vitro fertilization and related procedures. Hum. Reprod. 3, 161–164.

Yovich, J.L., Stanger, J.D., Yovich, J.M., Tuvic, A.I., Turner, S.R., 1985. Hormonal profiles in the follicular phase, luteal phase and first trimester of pregnancies arising from in vitro fertilization. Br. J. Obstet. Gynaecol. 92, 374–384.

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