ISSN: 2637-4617

Gratis

Research Article

Current Opinion in Gynecology and Obstetrics

The Neglected Luteal Phase after Natural Conception: Rescue by Early Progesterone Supplementation

Tesarik J[1*], Mendoza N[1,2] and Mendoza-Tesarik R[1,2]

[1]MARGen Clinic (Molecular Assisted Reproduction and Genetics), Granada, Spain
[2]University of Granada, Granada, Spain

***Correspondence:** Jan Tesarik, MARGen Clinic, Camino de Ronda 2, 18006 Granada, Spain, E-mail: jtesarik@clinicamargen.com

Received date: April 04, 2019; Accepted date: April 28, 2019; Published date: May 03, 2019

Abstract

Background: Luteal phase deficiency (LPD) was recognized as a potential cause of infertility well before the first attempts at ovarian stimulation and in vitro fertilization (IVF). However, in the subsequent IVF era, the fact that LPD is particularly frequent in the context of ovarian stimulation has driven the attention to LPD almost exclusively to stimulated cycles. Here we re-assess the role of LPD as the primary cause of infertility and suggest a possible solution.
Patients and Methods: This study involves 12 young couples with unexplained infertility who attended our clinic for an assisted reproduction attempt. All of the female partners had low serum progesterone concentrations on day 21 of their menstrual cycle, in spite of the presence on an apparently functional corpus luteum. The female patients underwent repeated ultrasound scans during three subsequent cycles to determine the day of spontaneous ovulation. They were counselled to have frequent sexual intercourse when the dominant follicle reached the size of >17 mm, and progesterone was administered daily, by vaginal route, in all of them beginning with the day on which ovulation had been confirmed.
Results: Out of the 12 women included in this study, six became pregnant naturally during one of the three progesterone-supplemented cycles. Progesterone supplementation was discontinued progressively, based on repeated serum progesterone determinations during the early pregnancy. All of the pregnancies were singleton. One of them ended in a miscarriage, while the others went to term, resulting in the birth of five normal children.
Conclusions: Our data suggest that LPD during natural ovulatory cycles may be more frequent than believed. In the present study, no other apparent causes of infertility were detected. In such cases, assisted reproduction techniques can be avoided and replaced by individualized progesterone supplementation during the early luteal phase.

Keywords: Luteal phase deficiency, Natural conception, Progesterone supplementation, Pregnancy rescue

Abbreviations: LPD: Luteal Phase Deficiency; IVF: In Vitro Fertilization; GnRH: Gonadotropin-Releasing Hormone; HCG: Human Chorionic Gonadotropin

Introduction

Luteal phase deficiency (LPD), characterized by insufficient secretion of progesterone by the corpus luteum, was first studied and treated by Georgeanna Seegar Jones in the 1940s [1,2], well before the beginning of the assisted reproduction era. It is known to be associated with ovarian stimulation protocols for in vitro fertilization (IVF), in general, and particularly with protocols that utilize a gonadotropin releasing hormone (GnRH) agonist as trigger [3,4]. On the other hand, it is currently considered to be a relatively infrequent cause of infertility in natural ovulatory cycles [5].

Midluteal phase serum progesterone level is currently the most widely used as a diagnostic tool for LPD. In spite of the pulsatile character of progesterone release from the corpus luteum, reflecting the pulsatile release of LH from the pituitary [6], a single serum progesterone level below 10 ng/ml, measured in the midluteal phase, is considered as a reliable indicator of LPD [7].

Evaluation of midluteal serum progesterone concentration is part of the standard evaluation of infertile couples before their inclusion in our assisted reproduction program. Here we report a series of 12 cases of unexplained infertility in which LPD appeared to be the main cause. The women were monitored for spontaneous ovulation detection in three consecutive cycles and counselled to have frequent sexual intercourse around the time of ovulation. Following ovulation their luteal phase was supported with exogenous progesterone administration in an attempt to achieve and maintain a natural pregnancy.

Patients and Methods

This retrospective study involved 12 women with a duration of infertility of between 2 and 3 years, attending our clinic for an assisted reproduction attempt in the period between September 2016 and December 2018. Their age ranged from 24 to 35 years, and all of them had a normal body mass index (20.1-24.7 kg/m^2), regular, normal-length (27-30 days) menstrual cycles and duration of infertility between 2 and 3 years (Table 1). Their ovarian reserve (Table 1), as judged by antral follicle count (12-21) and serum levels of anti-Müllerian hormone (2.9-5.0), was normal or slightly supranormal, according to the current criteria of ovarian reserve testing [8]. All of them had normal uterine cavity, as assessed by virtual sonographic hysteroscopy [9] and none showed signs of endometriosis. Apart from the history of unexplained infertility, the female partners of the couples included in this study shared one common feature, low serum concentrations of progesterone (<10 ng/ml), on Day 21 of the last unsupplemented cycle (Table 2), in spite of the presence of apparently normal corpus luteum detected by ultrasound on the same cycle day. Serum progesterone concentration was determined by a solid phase, competitive immunoassay using enzyme-labeled chemiluminescent technology (Immulite 1000 Progesterone, Siemens, Bellport, NY, USA).

The male partners were aged between 23 and 38 years, had normal sperm count, motility and morphology [10], and none of them had pathologically increased levels of sperm DNA fragmentation [11]. Couples with endocrine or systemic disorders that increased the risk of infertility, such as diabetes and pre-diabetes, abnormalities of thyroid gland function, autoimmune diseases, genetic defects, smoking and drug abuse, detected in one or both partners, were excluded from the study.

After careful examination of all potential causes of infertility, the couples were counselled to have three consecutive attempts at natural conception with ovulation-synchronized timed sexual intercourse and subsequent luteal phase support with exogenous progesterone supplementation. The day of ovulation was determined by repeated vaginal ultrasound scans, carried out every other day beginning with the 7th day of the menstrual cycle. The couples were advised to have frequent sexual intercourse when the dominant follicle had reached the size of 17 mm in diameter. The ultrasound examinations were continued to detect signs of ovulation. As soon as ovulation was confirmed, the patients were given 600 mg exogenous micronized progesterone (Utrogestan, Besins Healthcare, Monaco) daily by the vaginal route. This treatment was continued until the 28th day of the cycle, when serum β-HCG concentration was determined to detect pregnancy. In case of the positive pregnancy test, serum progesterone concentration was repeated once a week, and progesterone supplementation was continued until normal and stable progesterone concentrations were achieved. This time did not exceed two additional weeks from the time of ovulation in any case. Ultrasound pregnancy diagnosis was undertaken 6-7 weeks after the last menstrual period.

Results and Discussion

As compared with the last unsupplemented cycle, serum concentrations of progesterone in the first supplemented cycle were within the normal range (>10 ng/ml) in all women involved in this study (Table 2). Six of them became pregnant after the timed sexual intercourse. One of these pregnancies was achieved in the first progesterone-supplemented cycle, one in the second one and four in the third (Table 2). All pregnancies were singleton. One of the six pregnancies (Case 7) resulted in a miscarriage, and five normal babies were born.

These data suggest that LPD may be a cause of infertility in some couples in whom no other cause underlying fertility problems is identified either in the male or the female partner. This finding contradicts the opinion of the practice committee of the American

Table 1: Features of the women with luteal phase deficiency in spontaneous cycles, subsequently rescued by timely exogenous progesterone administration.

Case	Age	BMI	AFC	Serum AMH	Mean cycle duration	Infertility duration
	years	kg/m²		ng/ml	days	years
1	26	24.4	21	5	28	2
2	28	23.6	16	4.9	29	2
3	31	24	15	3.8	29	2
4	28	22.1	18	4.8	30	2
5	24	23.8	20	4.7	28	2
6	32	24.3	17	4.2	28	3
7	35	22.9	12	2.9	28	3
8	29	20.1	19	3.5	27	2
9	34	23.5	13	3.3	28	2
10	30	22	14	3.2	28	3
11	33	24.7	16	3.1	28	2
12	34	24.5	15	3.9	27	2

BMI: body mass index; AFC: antral follicle count in both ovaries on day 3-5 of menstrual cycle; AMH: anti-Müllerian hormone.

Table 2: Midluteal serum progesterone levels in the last unsupplemented cycle and the first progesterone-supplemented cycle, and pregnancy outcomes in the progesterone-supplemented cycles of the women with luteal phase deficiency.

Case	Day 21 serum progesterone ((ng/ml)		Pregnancy in 3 supplemented cycles
	Unsupplemented	Supplemented	
1	5.6	15.7	Yes, in the first cycle
2	6.8	14.1	No
3	4.1	12.5	No
4	7	15.6	Yes, in the third cycle
5	8.9	18	Yes, in the second cycle
6	7.7	13.6	Yes, in the third cycle
7	4.9	12.1	Yes, in the third cycle
8	7.5	14.2	No
9	6.6	12.8	No
10	8	12.9	No
11	9.3	18.3	Yes, in the third cycle
12	6.9	19	No

Society for Reproductive Medicine, which concluded that LPD, as an independent entity causing infertility, has not been proven [5]. The prevalence of this type of infertility was not evaluated in this study, but it appears to be low because more than two years, and more than 200 patients examined (after the exclusion of other possible causes of infertility) were needed to assemble the study group.

A recent study failed to prove a relationship between luteal phase length and infertility over a 12-month observation period [12]. Interestingly, none of the women included in our study showed abnormally short cycle length (Table 1), and an apparently normal corpus luteum was observed by vaginal ultrasound scan in all of them. These data suggest that the corpus luteum is formed after ovulation and persists for a usual time in women with LPD. However, for unknown reasons, its secretion of progesterone, though sufficient to maintain the secretary endometrium, is too low to enable the

establishment and maintenance of pregnancy. Another possibility is that secretion of progesterone from the corpus luteum is normal, but the secreted progesterone is excessively eliminated from serum by some, yet unknown mechanism. Further study is needed to address these issues.

In spite of the fact that an isolated LPD as a sole cause of infertility appears to be rare, it has to be taken into consideration. If it occurs in couples with otherwise unexplained infertility, the recourse to assisted reproduction may be avoidable, and the timed sexual intercourse with subsequent exogenous progesterone supplementation may be sufficient. Direct stimulation of the patient's corpus luteum by prolonged administration of GnRH agonist was shown to be useful to boost corpus luteum function both in GnRH antagonist-triggered [13,14] and HCG-triggered [15] ovarian stimulation cycles. The evaluation of the use of GnRH agonists to increase luteal-phase progesterone secretion in natural cycles of women with LPD, instead of direct exogenous progesterone administration, is an interesting challenge for future research.

Though rare as an isolated factor causing infertility, LPD can be masked by other associated factors compromising fertility, of both male and female origin. If it is not correctly diagnosed, it may contribute to assisted reproduction failures. In fact, the observation that some women have a tendency toward a dysfunctional luteal phase in stimulated cycles, regardless of the treatment used [16,17], can be explained by a masked intrinsic LPD upon which the more or less negative effects of different ovarian stimulation protocols are superimposed. It is thus important to evaluate midluteal phase serum concentrations of progesterone in all cases of infertility, irrespectively of its main cause, and to take the eventual presence of LPD in consideration as a pre-requisite for the choice of optimal ovarian stimulation protocol and luteal phase support. Low concentrations of pregnanediol-3-alpha-glucuronide in first morning urine samples taken during the luteal phase can also be used as a predictor of abnormal luteal phase [18].

In conclusion, the luteal phase concentrations of progesterone may still be neglected as a cause of infertility. If this condition is associated with other causes, for which an assisted reproduction treatment is indicated, its recognition can assist with selecting the optimal treatment protocol and help avoid unnecessary pregnancy losses. Post-ovulatory supplementation with progesterone as a treatment for LPD should be considered before attempting more invasive and extensive assisted reproductive procedures.

References

1. Astwood EB, Jones GES. A simple method for the quantitative determination of pregnanediol in human urine. *J Biol Chem*. 1941;137(1):397-407. http://www.jbc.org/content/137/1/397.citation
2. Jones GES. Some newer aspects of the management of infertility. *J Am Med Ass*. 1949;141(16):1123-1129. Doi: https://doi.org/10.1001/jama.1949.02910160013004
3. Beckers NGM, Macklon NS, Eijkemans MJ, et al. Non-supplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. *J Clin Endocrinol Metab*. 2003;88(9):4186-4192. Doi: https://doi.org/10.1210/jc.2002-021953
4. Fauser BCJM, Devroey P. Reproductive biology and IVF: Ovarian stimulation and luteal phase consequences. *Trends Endocrinol Metab*. 2003;14(5):236-242. Doi: https://doi.org/10.1016/S1043-2760(03)00075-4
5. Practice Committee of the American Society for Reproductive Medicine. Current clinical irrelevance of luteal phase deficiency: A committee opinion. *Fertil Steril*. 2015;103(4):e27-e32. Doi: https://doi.org/10.1016/j.fertnstert.2014.12.128
6. Filicori M, Butler JP, Crowley WF. Neuroendocrine regulation of the corpus luteum in the human. Evidence for pulsatile progesterone secretion. *J Clin Invest*. 1984;73(6):1638-1647. Doi: https://doi.org/10.1172/JCI111370
7. Jordan J, Craig K, Clifton DK, et al. Luteal phase defect: The sensitivity and specificity of diagnostic methods in common clinical use. *Fertil Steril*. 1994;62(1):54-62. Doi: https://doi.org/10.1016/S0015-0282(16)56815-0
8. Tal R, Seifer DB. Ovarian reserve testing: A user's guide. *Am J Obstet Gynecol*. 2017;217(2):129-140. Doi: https://doi.org/10.1016/j.ajog.2017.02.027
9. Tesarik J, Mendoza-Tesarik R, Mendoza N. Virtual ultrasonographic hysteroscopy followed by conventional operative hysteroscopy, enabling pregnancy. *Am J Obstet Gynecol*. 2017;216(2):188.e1. Doi: https://doi.org/10.1016/j.ajog.2016.09.081

10. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. *Hum Reprod Update*. 2010;16(3):231-245. Doi: https://doi.org/10.1093/humupd/dmp048
11. Tesarik J, Mendoza-Tesarik R, Mendoza C. Sperm nuclear DNA damage: Update on the mechanism, diagnosis and treatment. *Reprod Biomed Online*. 2006;12(6):715-721. Doi: https://doi.org/10.1016/S1472-6483(10)61083-8
12. Crawford NM, Pritchard DA, Herring AH, et al. Prospective evaluation of luteal phase length and natural fertility. *Fertil Steril*. 2017;107(3):749-755. Doi: https://doi.org/10.1016/j.fertnstert.2016.11.022
13. Bar-Hava I, Mizrachi Y, Karfunkel-Doron D, et al. Intranasal gonadotropin-releasing hormone agonist (GnRHa) for luteal-phase support following GnRHa triggering, a novel approach to avoid ovarian hyperstimulation syndrome in high responders. *Fertil Steril*. 2016;106(2):330-333. Doi: https://doi.org/10.1016/j.fertnstert.2016.04.004
14. Tesarik J, Mendoza-Tesarik R, Mendoza N. Gonadotropin-releasing hormone agonist for luteal phase support: The origin of the concept, current experience, mechanism of action and future perspectives. *Fertil Steril*. 2016;106(2):268-269. Doi: https://doi.org/10.1016/j.fertnstert.2016.04.034
15. Mendoza-Tesarik R, Mendoza N, López CC, et al. GnRH agonist treatment of luteal phase deficiency in HCG-triggered IVF cycles: A matched case-control study. *Reprod Biomed Online*. April 2019. Doi: https://doi.org/10.1016/j.rbmo.2019.03.215
16. Emperaire J, Parneix I, Ruffie A. Luteal phase defects following agonist-triggered ovulation: A patient-dependent response. *Reprod Biomed Online*. 2004;9(1):22-27. Doi: https://doi.org/10.1016/S1472-6483(10)62105-0
17. Abbara A, Clarke SA, Dhillo WS. Novel concepts for inducing final oocyte maturation in in vitro fertilization treatment. *Endocr Rev*. 2018;39(5):593-628. Doi: https://doi.org/10.1210/er.2017-00236
18. Abdulla SH, Bouchard TP, Leiva RA, et al, Ecochard R. Hormonal predictors of abnormal luteal phase in normally cycling women. *Front Public Health*. 2018;6. Doi: https://doi.org/10.3389/fpubh.2018.00144