ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Individualized luteal phase support normalizes live birth rate in women with low progesterone levels on the day of embryo transfer in artificial endometrial preparation cycles

Elena Labarta, M.D.,[a,c] Giulia Mariani, M.D.,[a,b] Cristina Rodríguez-Varela, Ms.C.,[c] and Ernesto Bosch, M.D.[a,c]

[a] IVIRMA Valencia, Valencia, Spain; [b] IVIRMA Roma, Roma, Italy; and [c] IVI Foundation, Valencia, Spain

Objective: To analyze the impact on live birth rates (LBRs) of the individualized luteal phase support (termed iLPS) in patients with low serum progesterone (P) levels compared with patients without iLPS.
Design: Retrospective cohort study, December 1, 2018, to May 30, 2019.
Setting: Private medical center.
Patient(s): A total of 2,275 patients checked for serum P on the day of blastocyst transfer were analyzed. During the study period, 1,299 patients showed serum P levels of ≥9.2 ng/mL, whereas 550 showed serum P levels of <9.2 ng/mL and received iLPS. Additionally, a historical group of 426 patients with serum P levels of <9.2 ng/mL but no iLPS were used for comparison.

Eligible patients were aged ≤50 years with adequate endometrium morphology after receiving estrogens. Luteal phase support was provided with micronized vaginal P (MVP) to all women. Patients with personalized initiation of exogenous P according to the endometrial receptivity assay test, polyps, fibroids distorting the cavity, or hydrosalpinx were not included in the analysis.
Intervention(s): As routine practice since December 2018, patients with low serum P levels received an iLPS with a daily injection of 25 mg of subcutaneous P from the day of embryo transfer (ET) in addition to standard LPS (400 mg of MVP twice a day).
Main Outcome Measure(s): Live birth rate.
Result(s): The LBR was 44.9% in the iLPS cases vs. 45.0% in patients with normal serum P levels (crude odds ratio [OR], 1.0; 95% confidence interval [CI], 0.82–1.22). By regression analysis, low serum P levels did not affect the LBR after adjusting for possible confounders (age, oocyte origin, fresh vs. frozen, day of ET, embryo quality, number of embryos transferred) (adjusted OR, 0.99; 95% CI, 0.79–1.25). Similarly, no differences were observed in other pregnancy outcomes between groups.

The LBR was significantly higher in the group of patients who received additional subcutaneous P (iLPS) compared with the historical group with low serum P levels and no iLPS (44.9% vs. 37.3%; OR, 1.37; 95% CI, 1.06–1.78).

In the overall population, patients showing P levels of <9.2 ng/mL on the day of ET were slightly younger and had higher body mass index and lower estradiol and P levels during the proliferative phase compared with patients with P levels of ≥9.2 ng/mL. No differences were observed with regard to the time in between the last dose of MVP and the serum P determination. After a multivariable logistic regression analysis, only body mass index and estradiol levels in the proliferative phase reminded statistically significant.

Significant differences in the LBR were observed between patients with serum P levels of <9.2 ng/mL without iLPS and patients with serum P levels of ≥9.2 ng/mL when using either own or donated oocytes.
Conclusion(s): Individualized LPS for patients with low serum P levels produces LBRs similar to those of patients with adequate serum P levels. (Fertil Steril® 2021;■:■–■. ©2021 by American Society for Reproductive Medicine.)
Key Words: Progesterone supplementation, hormone replacement therapy cycles, serum progesterone, luteal phase support, embryo transfer

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Reprint requests: Elena Labarta, M.D., IVIRMA Valencia. Plaza de la Policía Local, 3. 46015, Valencia, Spain (E-mail: elena.labarta@ivirma.com).

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Low serum progesterone (P) levels on the day of embryo transfer (ET) have been related to a negative impact on pregnancy outcome in artificial endometrial preparation cycles when using micronized vaginal P (MVP), according to the first prospective blinded study that analyzed this relationship (1). We observed that those patients with serum P levels of <9.2 ng/mL (corresponding to the 25th percentile) had a 20% lower ongoing pregnancy rate (OPR) than those with a higher P level. Additional retrospective studies have since confirmed that a minimum level of serum P has to be reached in the midluteal phase to optimize outcomes (2, 3).

The negative clinical impact of low serum P levels prompted two questions: would initial findings, which were tested in oocyte donation cycles, also be applicable in patients treated with own eggs; and could this negative effect be resolved by assessing low P levels on the day of ET and increasing the dose of P accordingly, thus avoiding cycle cancellation?

To answer the first question, we conducted a second prospective study enrolling 1,205 patients with own or donated oocytes (4). We confirmed that patients with low P levels yielded a significantly lower OPR (−17.8%), lower live birth rate (LBR) (−16.5%), and higher clinical miscarriage rate (+9.5%) (4). For the second one, we implemented a straightforward individualization of LPS, termed individualized luteal phase support (iLPS) (5), and analyze its impact on the LBR. Individualized LPS comprised administering a daily injection of subcutaneous P (SCP) when low serum P levels were detected on the day of ET; this supplemented the MVP already administered during endometrial preparation. Subcutaneous P was used instead of additional MVP dosage to avoid vaginal discharge and to offer a different option to patients who may have limited vaginal absorption.

We hypothesized that augmenting serum P levels by increasing doses of exogenous P may improve the pregnancy outcome in women with low P levels. The present study compared the LBR of patients with low P levels on the day of ET, in whom iLPS was performed, with that of patients who had adequate serum P levels on the day of ET during the study period. Additionally, the results were compared with a historical group of patients with low serum P levels but not receiving iLPS.

MATERIALS AND METHODS

Study Design

This retrospective cohort study was conducted at a private in vitro fertilization center (IVIRMA Valencia, Spain) from December 1, 2018, to May 30, 2019. A historical group of patients (included period from March 2016 to November 2018) were used for comparison.

Ethics

This study was approved by the Institutional Review Board at IVI Valencia, Spain. The Spanish agency of medicines and medical devices cataloged the study as a postauthorization study with retrospective analysis (approval number: IVI-PRO-2018-01).

Study Population

Eligible patients were women aged ≤50 years with an adequate endometrial pattern (triple layer) and thickness (≥6.5 mm) after receiving estrogens in the proliferative phase and LPS with only micronized P administered vaginally (400 mg/12 hours for 5 days; Utrogestan; SEID, Barcelona, Spain) before ET, regardless of gamete origin. All patients were transferred a maximum of two blastocysts under ultrasound guidance. Patients with personalized initiation of exogenous P according to the endometrial receptivity assay test, polyps, fibroids distorting the cavity, or hydrosalpinx were not included in the analysis.

Endometrial preparation with hormonal replacement therapy (HRT) is described elsewhere (1). Serum P measurements were taken on the day of ET approximately 6 ± 2 hours after the last insertion of MVP. The results were available the same day, approximately 2 hours after blood extraction.

As part of routine practice since December 1, 2018, patients with midluteal serum P levels of <9.2 ng/mL received supplemental P in the form of a subcutaneous (SC) injection of 25 mg of P (Prolutex; Angelini Pharma, Spain) once daily. This extra dose of P was administered between the two vaginal MVP doses (i.e., 6 hours apart of both intakes). The cutoff level (9.2 ng/mL) was chosen according to the results of our first published prospective study (1). Luteal phase support was maintained until pregnancy week 12 or until the day of pregnancy test if negative (Fig. 1).

We analyzed the pregnancy outcome of 550 women who showed low serum P levels on the day of ET and received an additional daily injection of 25 mg of SCP from the day of ET. The results were compared with those of a group of patients having adequate serum P levels (≥9.2 ng/mL) on the day of ET (n = 1,299) who received only MVP (400 mg/12 hours) during the study period. Additionally, we include the historical data of patients having inadequate serum P levels (<9.2 ng/mL) and not receiving iLPS (n = 426). This group also included patients with own and donated oocytes.

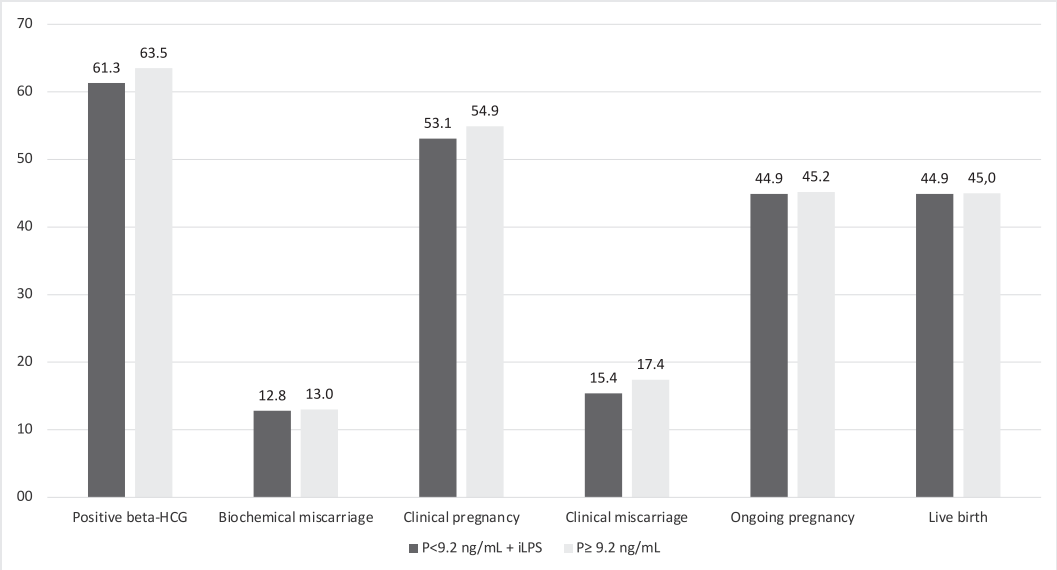
Vitrification, Warming, and ET Protocols

Blastocysts were cryopreserved using the Cryotop vitrification protocol, as previously described elsewhere (6). Solutions employed were those marketed by KITAZATO BioPharma, Tokyo, Japan. No more than one blastocyst per Cryotop was loaded, and embryos were stored in vapor tanks (V1500-AB Isothermal Freezer) (Custom Biogenic Systems, Bruce Township, Michigan) for a variable storage time. Warming took place in the morning of the cryotransfer day. After warming, blastocysts were cultured for 2–4 hours until the embryos were transferred. Blastocyst survival was evaluated after warming on the basis of morphology and the ability of the blastocoel to re-expand before ET.

P Analysis

Blood samples were analyzed by an electrochemiluminescence immunoassay (Cobas e411 analyzer; Roche Diagnostics GmbH, Germany). The intraassay and interassay coefficients of variation for P determinations were 1.2%–11.8% and

FIGURE 1



Clinical outcomes of patients with serum P levels of <9.2 ng/mL and following an individualized luteal phase support (dark bars) compared with those of patients with serum P levels of ≥9.2 ng/mL (light bars).

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3.6%–23.1%, respectively, for P levels between 0.22 ng/mL and 51.6 ng/mL. Sensitivity was 0.03 ng/mL. This assay was used also during the period in which the patients in the historical control group were treated.

Main Outcomes

The primary objective was to compare the LBR observed in patients with low serum P levels on the day of ET in which the iLPS strategy was conducted, with patients without iLPS, with either low or high P levels according to the defined threshold. Live birth was considered delivery that resulted in at least one live born neonate. The secondary endpoints were as follows: positive beta human chorionic gonadotropin (β-hCG) test (serum β-hCG levels of >10 IU/mL 11 days after ET); clinical pregnancy (presence of at least one intrauterine gestational sac on ultrasound); ongoing pregnancy (presence of at least one viable fetus beyond week 12); biochemical miscarriage (positive β-hCG test without evidence of a gestational sac); clinical miscarriage (pregnancy loss after confirmation of an intrauterine gestational sac); and ectopic pregnancy (gestational sac located outside the uterine cavity).

Following our routine practice, an automated questionnaire was sent 1 month after the expected date of delivery to report the obstetric and perinatal data.

Statistical Analyses

Continuous variables are expressed as mean and SD, whereas categorical variables are expressed as percentage. Serum P level was analyzed as both a continuous variable and a dichotomous variable (normal or low according to the cutoff of 9.2 ng/mL on the basis of our previous study (1)). Univariate comparisons between the study and control groups were performed with either the χ^2 and Fisher's exact test for categorical variables or t test for continuous variables. Multivariate logistic regression analysis was conducted to analyze the impact of having serum P levels of <9.2 ng/mL on the LBR after adjusting for confounding variables (all those showing a P value of <.2 in the previous univariate analysis for the LBR: fresh vs. frozen, day of ET, embryo quality, number of embryos transferred) as well as age and origin of oocytes, as forced-in variables. Additionally, a multivariate analysis was conducted for detecting which factors can influence having serum P levels of <9.2 ng/mL, after adjusting for confounding factors (age, weight, height, time between last dose of P and blood test, days on estrogens, and last serum estradiol [E2] and P levels measured in the proliferative phase). P values < .05 were considered statistically significant. Statistical package SPSS 25.0 (IBM Corp., Armonk, New York) was used for all statistical analyses.

RESULTS

During the study period, a total of 1,849 eligible patients for whom a blastocyst transfer was performed after artificial endometrial preparation were checked for serum P on the day of ET. Overall, the mean serum P levels on the day of ET were 12.9 ± 9.0 ng/mL. Serum P was measured within a mean time of 6.4 ± 2.5 hours after the last insertion of MVP. The overall positive β-hCG rate was 62.8% (95% confidence interval [CI], 60.6–65.1), with an LBR of 44.9% (95% CI, 43.0–47.2).

Of the overall population, 550 patients (29.7%) showed serum P levels of <9.2 ng/mL. All of them consented to receive SCP from the day of ET.

Patients with Low Serum P Levels and iLPS vs. Patients with Normal Serum P Levels

Patients with serum P levels of <9.2 ng/mL and iLPS had significantly higher weight and body mass index (BMI) and showed lower E2 levels in the proliferative phase compared with patients with higher P levels (Table 1; all differences $P<.001$).

When comparing the LBR between both populations, no differences were observed (LBR was 44.9% in patients with iLPS vs. 45.0% in the controls; crude odds ratio [OR], 1.0; 95% CI, 0.82–1.22; $P=1.0$). Similarly, all other clinical outcomes did not show any significant differences (Fig. 1).

Univariate analysis showed that the LBR was significantly higher when transferring fresh embryos (51.8% fresh vs. 42.2% frozen), day 5 blastocysts (47.2% day 5 vs. 34.9% day 6), good-quality blastocysts (48.6% A or B vs. 29.5% C according to the Spanish Association for the study of Reproductive Biology classification [7], $P<.001$). The mean number of embryos transferred was 1.12 ± 0.3 in patients with a live birth vs. 1.08 ± 0.3 in patients without live birth ($P=.01$). No differences were observed in the LBR between own and donated origin of oocytes (45.7% vs. 44.6%, $P=.665$, respectively).

Regression analysis for LBR showed that low serum P levels did not affect LBR after adjusting for possible confounders, such as age, origin of oocytes, fresh vs. frozen, day of ET, embryo quality, and number of embryos transferred (adjusted OR, 0.99; 95% CI, 0.79–1.25; $P=.96$) (Fig. 3).

Patients with Low Serum P Levels and iLPS vs. Patients with Low Serum P Levels and no iLPS (Historical Group)

The patients included in the present study who followed a rescue treatment (iLPS) when the serum P level was <9.2 ng/mL on the day of ET (n = 550) were slightly older (40.5 ± 5.0 vs. 39.5 ± 4.6, $P=.002$) and underwent more frequently an oocyte donation treatment (68.9% vs. 59.4%, $P=.002$) than the historical group of patients who did not follow a rescue treatment when the serum P level was <9.2 ng/mL (n = 426) (Table 2).

Serum P during the proliferative phase was higher in the iLPS group (0.20 ± 0.21 vs. 0.16 ± 0.20, $P=.037$) as well as on the day of ET (7.0 ± 1.7 vs. 6.6 ± 1.9, $P=.005$). The number of embryos transferred was slightly lower in the rescued group (1.1 ± 0.29 vs. 1.2 ± 0.39, $P=.040$), and the time in between the last dose of MVP and ET was 1 hour longer in this group (6.7 ± 2.4 vs. 5.7 ± 2.5, $P=.007$) (Table 2).

The LBR was significantly higher in the group of patients who received additional SCP (44.9% vs. 37.3%; OR, 1.37; 95% CI, 1.06–1.78; $P=.018$) (Fig. 2). When submitted to a

TABLE 1

Comparison of patients with serum P levels of < 9.2 ng/mL and individualized luteal phase support (iLPS) vs. patients with serum P levels of ≥9.2 ng/mL. Baseline demographic characteristics according to the group.

	P level < 9.2 ng/mL + iLPS (n = 550)	P level ≥ 9.2 ng/mL (n = 1,299)	*P* value
Age	40.5 ± 5.0	40.5 ± 4.9	.888
BMI (kg/m^2)	24.1 ± 4.5	23.0 ± 3.9	.000
Weight (kg)	65.5 ± 12.6	62.9 ± 11.5	.000
Height (m)	1.64 ± 0.1	1.65 ± 0.1	.163
Endometrial thickness (mm)	8.8 ± 1.8	8.7 ± 1.8	.767
E2 in the proliferative phase (pg/mL)	246.6 ± 184.2	300.4 ± 340.0	.000
P in the proliferative phase (ng/mL)	0.20 ± 0.21	0.22 ± 0.25	.278
Days on HRT until ET	17.8 ± 4.6	18.0 ± 4.5	.532
Origin of oocytes			
Own	30.1%	30.6%	.847
Donated	68.9%	69.4%	
No. of embryos transferred	1.1 ± 0.29	1.1 ± 0.30	.624
Day of blastocyst (n; %)			
Day 5	81.1%	82.2%	.291
Day 6	18.9%	17.8%	
PGT-A cycles	21.5%	19.9%	.448
Embryo quality			
Grade A or B (GQe)	80.6%	83.7%	.135
Grade C	19.4%	16.3%	
Serum P level on the day of ET (ng/mL)	7.0 ± 1.7	15.4 ± 9.6	.000
Hours between the last dose of MVP and blood analysis ET	6.7 ± 2.4	6.2 ± 2.6	.521
Fresh (only from donors)	26.4%	29.3%	.114
Frozen	73.6%	70.7%	

Note: BMI = body mass index; ET = embryo transfer; E2 = estradiol; HRT = hormonal replacement therapy; MVP = micronized vaginal progesterone; P = progesterone; PGT-A = preimplantation genetic testing for aneuploidy.

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multivariable logistic regression analysis to adjust for all confounding factors, the differences between both groups remained statistically significant with an OR of 1.65 (95% CI, 1.06–2.57) (Supplemental Fig. 1).

Clinical Factors Affecting Serum P Levels on the Day of ET

Patients with serum P levels of <9.2 ng/mL on the day of ET (both those who underwent iLPS and those who did not [n = 976]) were slightly younger (40.04 vs. 40.5 years old) and heavier (BMI, 24.1 vs. 23.1 kg/m^2) than those with serum P levels of ≥9.2 ng/mL. They also had lower E2 (248.6 vs. 300.4 pg/mL) and P (0.17 vs. 0.22 ng/mL) levels during the proliferative phase of the endometrial preparation. No differences were observed with regard to the time in between the last dose of MVP and the serum P determination (6.3 vs. 6.2 hours, P=.224; Supplemental Table 1, available online). After a multivariable logistic regression analysis, only BMI (P<.001) and E2 levels in the proliferative phase (P=.007) remained statistically significant.

Significant differences in the LBR were observed between patients with serum P levels of <9.2 ng/mL without iLPS and patients with serum P levels of ≥9.2 ng/mL when using either own (P=.04) or donated (P=.05) oocytes, as seen in Supplemental Table 2.

All pregnant patients responded to the automated questionnaire sent after the pregnancy to report the obstetric and perinatal data. There were three cases of perinatal death (all of them in the control group) and seven ectopic pregnancies (five were in the control group).

DISCUSSION

This retrospective analysis determined that patients with low serum P levels on the day of ET can have similar LBRs to those with adequate levels when a subcutaneous P dose is added to LPS from the day of ET. When this intervention was not performed, the LBRs were significantly lower. This finding facilitates the management of patients undergoing an ET in hormone replacement cycles because iLPS can be applied in the midluteal phase without hampering the results. Our findings confirm that the negative impact of low serum P levels occurs in either own or donated oocyte treatments, as suggested in our previous prospective study (4).

Clinical evidence suggests that serum P levels are a good marker of the bioactivity of exogenous P when using MVP (1–3, 8). This is relevant in artificial cycles, as exogenous P is used to compensate for the lack of a corpus luteum producing endogenous P (9). Because P is crucial to enhance embryo implantation and pregnancy maintenance (10), it is significant to ensure a good absorption of P and that a minimum threshold is reached to optimize pregnancy rates.

In our initial report, we observed such a strong correlation between serum P and pregnancy outcome to warrant an intervention in patients with low P levels (1). Previous studies demonstrated that increasing doses of vaginal P could reduce

TABLE 2

Comparison of patients with serum P levels of <9.2 ng/mL and individualized luteal phase support (iLPS) vs. a historical group of patients with serum P levels of <9.2 ng/mL who did not follow iLPS.

	P level < 9.2 ng/mL + iLPS (n = 550)	P level < 9.2 ng/mL and no iLPS (historical group, n = 426)	*P* value
Age	40.5 ± 5.0	39.5 ± 4.6	.002
BMI (kg/m^2)	24.1 ± 4.5	24.2 ± 4.4	.840
Weight (kg)	65.5 ± 12.6	65.2 ± 12.1	.739
Height (m)	1.64 ± 0.1	1.64 ± 0.1	.209
Endometrial thickness (mm)	8.8 ± 1.8	8.8 ± 1.5	.963
E2 in the proliferative phase (pg/mL)	246.6 ± 184.2	250.5 ± 170.5	.768
P in the proliferative phase (ng/mL)	0.20 ± 0.21	0.16 ± 0.20	.037
Days on HRT until ET	17.8 ± 4.6	17.8 ± 4.0	.910
Origin of oocytes (n; %)			
Own	31.1%	40.6%	.002
Donated	68.9%	59.4%	
No. of embryos transferred	1.1 ± 0.29	1.2 ± 0.39	.040
Day of blastocyst			
Day 5	81.4%	75.4%	.105
Day 6	18.6%	24.6%	
PGT-A cycles	21.5%	28.2%	.016
Embryo quality			
Grade A or B (GQe)	80.6%	78.2%	.378
Grade C	19.4%	21.8%	
Serum P level on the day of ET (ng/mL)	7.0 ± 1.7	6.6 ± 1.9	.005
Hours between the last dose of MVP and blood analysis	6.7 ± 2.4	5.7 ± 2.5	.007
ET			
Fresh (only from donors)	26.4%	14.1%	
Frozen	73.6%	85.9%	.000

Note: BMI = body mass index; ET = embryo transfer; E2 = estradiol; HRT = hormonal replacement therapy; MVP = micronized vaginal progesterone; P = progesterone; PGT-A = preimplantation genetic testing for aneuploidy.

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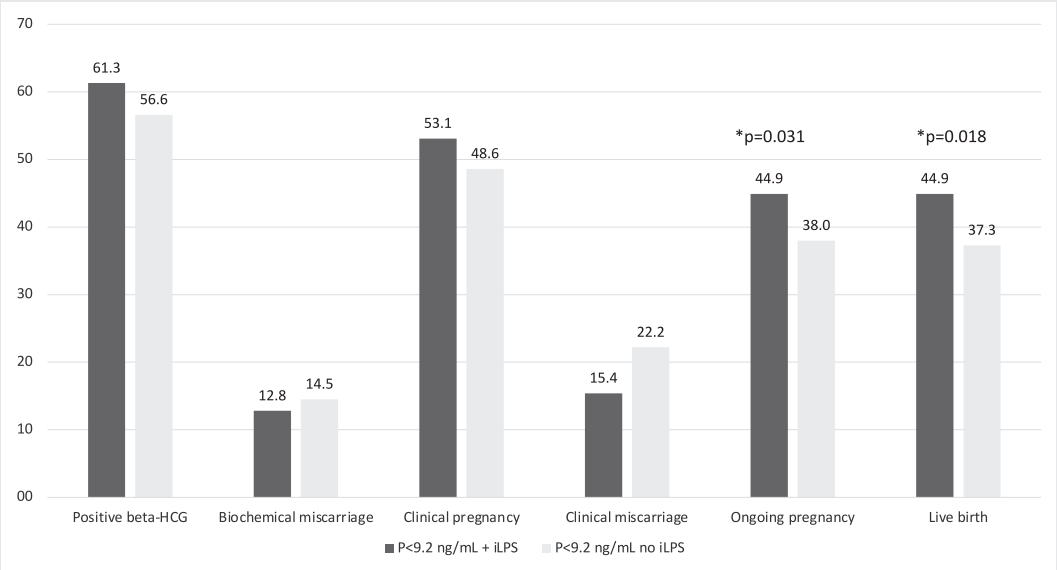
FIGURE 2



Clinical outcomes of patients with serum P levels of <9.2 ng/mL and following an individualized luteal phase support (iLPS) (dark bars) compared with a historical group of patients with serum levels of <9.2 ng/mL but not following an iLPS (light bars).

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the rate of miscarriage and increase pregnancy rate (11–13), although the serum P level was not measured. Accordingly, we sought to increase the exposure to exogenous P in those women with low levels, as a straightforward approach to this problem. The cutoff level (9.2 ng/mL) was chosen according to our initial published results (1) because analysis of data from the second study (4) was pending when we designed the current study. We chose a single daily injection of SCP to supplement LPS on the basis of our previous experience in a small set of patients (data not published) with a history of low serum P levels in a previous failed cycle, who had better outcomes when adding SCP in a subsequent cycle: serum P levels were significantly higher, and pregnancy outcome was similar to that in patients with normal levels. On the other hand, the fact that the live birth outcomes of the historical group of patients with low P levels and no intervention did not compare favorably with the contemporaneous intervention group reinforces the efficacy of this approach.

A daily dose of 25 mg of SCP achieves an adequate predecidual transformation of the endometrium (14), but it is not known if this is sufficient to fulfill the need for LPS in artificial cycles. In our study, we did not use SCP alone but in combination with MVP. Therefore, we do not know whether switching exclusively to SCP in cases of low P levels would be sufficient. The safety and efficacy of SCP are similar to vaginal preparations, although studies demonstrating this profile were performed in stimulated in vitro fertilization cycles (15, 16). Patient acceptance and satisfaction of subcutaneous injections are generally high because of the ease of use, little pain, and the possibility of self-medication compared with intramuscular injections (17).

In line with our findings, two recent studies have shown a positive effect of adding one single injection of 25 mg of SCP in patients with low serum P levels in the context of HRT cycles (18, 19). Our study reinforces this strategy and offers a higher sample size and the data from the historical group of patients with low serum P levels and not having received the iLPS.

According to our experience and reported data, 25%–30% of women have low serum P levels in the midluteal phase when LPS is performed with 400 mg of MVP twice a day, meaning that one out of three to four patients may be undertreated. Most importantly, these low levels are significantly associated with lower OPR. Why P levels are lower in some patients when receiving the same MVP dose is unknown, but there may be poor vaginal absorption of P or an effect of the frequency of sexual intercourse in some instances (20). Recent data suggest a negative relationship between weight, age, and the time of blood sampling and serum P levels (21). According to our data and once adjusted in a multiple regression analysis, only body weight and, hence, BMI were related to serum P levels. These patients also showed lower serum E2 levels during the proliferative phase, suggesting that this finding could be related to a lower hormone bioavailability in these patients.

The strengths of our study are that we included a large sample of infertile patients undergoing blastocyst transfer in artificial cycles in our clinic, which allows us to draw a conclusion on the efficacy of this strategy. More importantly,

we demonstrated that cancelling the cycle is not necessary and the measurement of serum P does not need to be performed in advance but can be conducted on the same day of ET, which facilitates the management of patients traveling to the clinic from long distances.

Although multiple regression analysis has been performed to minimize it, the main limitations of this study are the retrospective nature and the potential for bias because of other confounders. Further, in most patients, we did not measure serum P levels again after ET to confirm an increase from the extra supplementation. We could not find an association of the time between the last insertion of MVP and blood sampling with serum P levels. However, the range of this timing was not very wide in our practice as we recommend to measure serum P approximately 6 hours after the last insertion of exogenous P. Hence, this finding should be further explored and considered when making decisions on when to introduce the iLPS.

This study confirms that the addition of subcutaneous P proves to be effective in patients with low P levels, facilitating streamlined and cost-effective patient treatment.

CONCLUSION

The addition of exogenous P on the day of ET improves pregnancy rates in cases with low serum P levels, providing a simple, safe, and effective strategy to treat patients with low serum P levels in HRT cycles with MVP.

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