

The utility of detecting ovulation to predict success in ovulation induction and intrauterine insemination cycles — a prospective observational study

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ABSTRACT

Objectives: The success of ovulation induction-intrauterine insemination (OI-IUI) procedures may be limited by the absence of ovulation detection. The aim of this study was to evaluate the empirical use of ultrasonography and luteal phase progesterone (P4) as ovulation indicators and determine its effect on pregnancy outcome in OI-IUI cycles.

Material and methods: This prospective observational study, which was performed in a university setting, included 107 women with unexplained infertility. Following OI, IUI was performed 36 hours after human chorionic gonadotropin (hCG). P4 was measured 72–96 hours after hCG. At the same time, the appearance of ovaries and signs indicative of ovulation, which are decreased follicle dimensions, irregularity of follicular walls, and the presence of free fluid in the Douglas pouch, were noted.

Results: In 58 patients (54.2%), ovulation was detected at the P4 level of > 10 ng/mL. Eighty-nine patients had ultrasound images suggestive of ovulation. However, only 50 of these were confirmed ovulation as indicated using P4. Implantation was observed in a total of 13 patients (12.1%). All patients were in the ovulation detected group with P4 > 10 ng/mL (AUC: 0.750; p = 0.004). P4 of > 21.5 ng/mL detected successful ovulation and was strongly associated with implantation with 77% sensitivity and 61% specificity (OR: 9.9; 95% CI: 2.4–41.2). Body mass index (BMI) > 23.9 kg/m² was a reliable anovulation indicator as a secondary outcome (AUC: 0.696; p = 0.02).

Conclusions: In 45.8% of the patients, ovulation did not occur even with OI treatment. The association of progesterone measurement and ovarian ultrasound scanning between 72 and 96 hours after hCG treatment can be used to detect ovulation. In doing so, we can find the optimal treatment for patients with infertility in their next cycle.

Key words: ovulation; ovulation induction; progesterone; implantation; intrauterine insemination

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INTRODUCTION

One in six couples is affected by fertility disorders and approximately 30% of the patients in reproduction physicians experience unexplained infertility [1]. Ovulation induction (OI) followed by intrauterine insemination (IUI) is the first choice treatment of idiopathic infertility due to its low risk and cost-effectiveness [2]. The success of OI-IUI may vary from 8 to 20% according to maternal age, the follicular stimulation protocol, the timing of IUI, and the verification of ovulation [3]. Considering the lack of ovulation verification

following OI-IUI in current clinical practice, there is doubt that a luteinised unruptured follicle, despite treatment, may limit the success of the procedure [4].

IUI procedure should be performed at the time of follicle rupture [5]. Real-time and non-invasive evidence of ovulation offered by ovarian ultrasound has been previously described in women [6]. It involves disappearance or a decrease in follicle dimension, irregularity of follicular walls, and the presence of free fluid in the Douglas pouch. However, the use of ultrasonographic criteria for the detec-

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tion of ovulation is not a routine step for OI-IUI cycles in current practice [5].

Luteal progesterone (P4) is essential for endometrial receptivity and pregnancy maintenance [7]. Therefore, plasma P4 concentration is a low cost and reliable indicator of ovulation in humans. The level of P4 remains under 1 ng/mL during the follicular phase and progressively increases following the luteinising hormone (LH) surge, reaching maximum values between days seven and eight post-ovulation [1].

Objectives

In this study, our objective was to examine whether luteal phase progesterone levels and ultrasound indicators of ovulation on TVUS could predict successful implantation and clinical pregnancy in OI + IUI cycles.

MATERIAL AND METHODS

This was a prospective observational study conducted in a university setting. The study was approved by the Ethics Committee of Istanbul University School of Medicine (Date: June 21st, 2013, No.12).

Participant characteristics

One hundred fifteen patients undergoing OI-IUI treatment in Istanbul University infertility outpatient clinics were initially enrolled in the study. All participants underwent a detailed gynaecology examination, comprehensive infertility assessment including hysterosalpingography (HSG), ovarian reserve tests, mid-luteal P4 concentrations, and semen analysis. The inclusion criteria of the study were as follows: failure to conceive for at least 12 months of regular intercourse, spontaneous menstrual cycle regularity ranging from 21 to 35 days, bilateral tubal patency detected with HSG, basal (menstrual cycle day 3), follicle-stimulating hormone (FSH) levels under 15 IU/L, and normal semen characteristics according to the World Health Organization [8]. The exclusion criteria were as follows: moderate to severe endometriosis diagnosed as American Fertility Society, stage III or IV; the presence of a congenital uterine anomaly: abnormal prolactin or thyroid hormone levels; and male factor. Body mass indexes (BMI) of the patients were also noted.

Ovulation induction plus intrauterine insemination

Transvaginal ultrasound (TVUS) examinations were performed on all participants on day three of their menstrual cycle. After ruling out persistent follicles, they were treated with either clomiphene citrate (CC) for five days (Klomen, Kocak Farma, Turkey) or 75 IU recombinant FSH (Gonal-F, Organon, Turkey). Endometrial thickness and ovarian response were evaluated using TVUS starting from cycle day 7. If the diameter of any follicle did not reach 10 mm on cycle day nine, the gonadotropin (Gn) dose was increased by 50%.

If the diameter of the leading follicle reached 12 mm, the dose of gonadotropin remained the same until the day of human chorionic gonadotropin (hCG) trigger. When the dominant follicle reached 18 mm, triggering of ovulation by 250 µg recombinant hCG (Ovitrelle, Serono, Turkey) was performed.

Sperm for insemination was obtained via masturbation. Whole semen was washed and complemented with 0.5% human serum albumin in a 5-mL Falcon conical tube. This integrity was centrifuged at 1500 rpm for 5 min. The supernatant was rejected, and the pellet resuspended in 0.5 mL medium. 0.5 mL medium was coated on the suspension of sperm and the tube was sloped at 45 degrees angle and incubated at 37°C for at least 40 min. The tube was set gently, and the upper interface was aspirated with a Pasteur pipette. The supernatants of both tubes were collected for 0.4 cc sperm samples.

Cycles were cancelled when 3 or more dominant follicles were obtained and/or estradiol levels exceeded 1500 pg/mL. IUI was performed 36 h after the hCG application using a disposable intrauterine catheter. Luteal phase progesterone support was not administered. Serum P4 was measured 96 h after hCG administration. This was designated as the luteal phase P4. At the same time (96 h after hCG), TVUS was performed, and the appearance of ovaries and signs indicative of ovulation were noted.

When serum P4 was measured > 10 ng/mL, it was accepted as ovulation [9]. Twelve days after the IUI procedure, beta-hCG was measured. Serum beta-hCG levels above > 10 mIU/mL were accepted as "implantation". Six weeks after the IUI procedure, the presence of intrauterine fetal cardiac activity was accepted as "clinical pregnancy".

Statistical analysis

The statistical evaluation of our data was performed using the Statistical Package for the Social Sciences (SPSS version 15.0) (IBM Corp. Armonk, NY, USA) statistical software. The Kolmogorov-Smirnov test was used to assess the normality distributions of continuous variables. Regression and correlation analyses were performed to assess the relationship of variables concerning "ovulation", "implantation", and "clinical intrauterine pregnancy". Continuous variables were compared using the Mann Whitney-U test between groups with and without clinical pregnancy. We performed receiver operating characteristic curve (ROC) analysis to show the predictive value of the variables "Luteal P4" and "BMI" included in the model in regarding ovulation. The analysis of ROC curves provides values for the area under the curve (AUC), which vary between 0.5 and 1.0, and may be evaluated as estimations of the global classification ability of the model. Values are given in terms of 95% confidence intervals (CIs) and $p < 0.05$ as statistical significance.

RESULTS

Initially, 115 patients were enrolled in this prospective observational study. A total of eight patients were excluded from the study; two patients did not develop follicles > 18 mm, one patient could not adapt to treatment, two patients had cycle cancellations due to multi-follicular development, and three patients exceeded 96 hours after hCG. One hundred seven patients were included in the final analysis.

In our cohort, the mean age and BMI of the participants were 28.3 ± 4 years and 25.3 ± 3.9 kg/m², respectively. The mean basal hormone levels were as follows: FSH: 5.9 ± 2.6 mIU/mL, LH: 7.1 ± 5.2 IU/L, and anti-mullerian hormone (AMH): 3.5 ± 3.2 ng/mL. A total of 46 patients received 50 mg CC-IUI, 61 patients received Gn-IUI treatment.

Ovulation confirmed by luteal P4 > 10 ng/mL was verified in 58 patients out of 107. The patients were grouped according to the treatment protocols as the CC-IUI group (22/46, 47.8%) and the Gn-IUI group (36/61, 59%). The difference between the CC-IUI and Gn-IUI treatment groups was not statistically significant ($p = 0.238$). Eighty-nine patients out of 107 had ultrasound images suggestive of ovulation on TVUS; however, only 50 of these were confirmed ovulation confirmed according to serum P4 levels (Tab. 1).

Implantation was observed in a total of 13 patients (12.1%). All patients were in the ovulation detected group with luteal phase P4 > 10 ng/mL (AUC: 0.750; $p = 0.004$). ROC analysis showed that luteal phase P4 levels of > 21.5 ng/mL detected successful implantation with 77% sensitivity and 61% specificity (OR: 9.9; 95% CI, 2.4–41.2) (Fig. 1 and 2). Five patients in the CC-IUI group and five in the Gn-IUI group had fetal cardiac activity-positive pregnancies. Luteal phase P4 levels of 21.5 ng/mL were found significant in clinical pregnancy prediction with 90% sensitivity and 61% specificity (AUC: 0.810; $p = 0.001$). Two patients in the Gn-IUI group developed ectopic pregnancies. One was treated with single-dose methotrexate, the other underwent laparoscopic salpingectomy. One patient who achieved pregnancy in

the Gn-IUI group developed mild ovarian hyperstimulation syndrome and was treated conservatively.

As a secondary outcome, BMI was a reliable indicator of anovulation (AUC: 0.696; $p = 0.02$) (Tab. 2). Except for this, progesterone on the day of the hCG trigger was > 1 ng/mL in

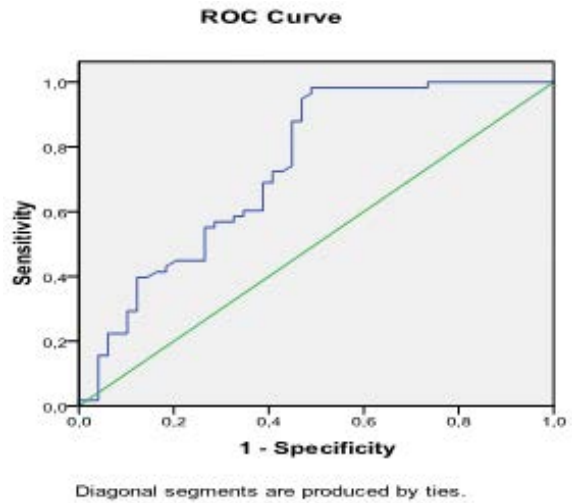


Figure 1. The relation of luteal phase progesterone and ovulation is shown above. Luteal phase P4 level of 21.5 ng/mL was found significant in clinical pregnancy prediction with 90% sensitivity and 61% specificity (AUC: 0.810; $p = 0.001$)

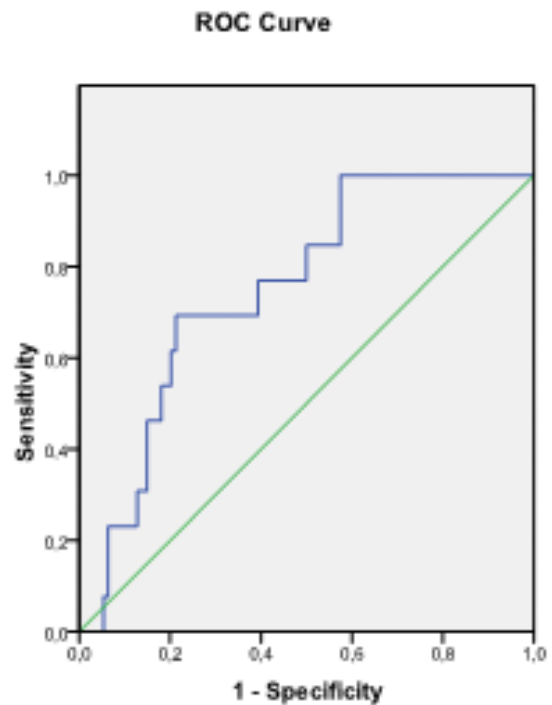


Figure 2. The correlation between luteal phase progesterone and implantation is shown. The ROC analysis showed that luteal phase P4 level of > 21.5 ng/mL detected successful implantation with 77% sensitivity and 61% specificity (OR: 9.9 [2.4–41.2])

Table 1. Comparative luteal phase progesterone levels and ultrasound characteristics

Progesterone [ng/mL]	Endometrial measurement [mm]	Evidence of ovulation on TVUSG* (n)	Evidence of anovulation on TVUSG** (n)
Progesterone > 10 ng/mL	< 8 mm	1	2
	> 8 mm	49	6
Progesterone < 10 ng/mL	< 8 mm	2	1
	> 8 mm	37	9
Total		89	18

*Disappearance or decrease in follicle dimensions, irregularity of follicular walls or presence of free fluid in the Douglas pouch is described as evidence of ovulation on TVUSG;

**Persistence of follicle is described as evidence of anovulation on TVUSG

12 patients. None of these patients with progesterone levels above 1 ng/mL achieved implantation/pregnancy despite two of these patients having signs suggesting ovulation on TVUS.

According to our correlation analysis, ovulation was negatively correlated with BMI ($r = -0.293$; $p = 0.002$) and serum FSH ($r = -0.204$; $p = 0.04$), and positively correlated with hCG day P4 ($r = 0.411$; $p < 0.001$), luteal phase P4 ($r = 0.347$; $p < 0.001$). Implantation was negatively correlated with serum FSH levels ($r = -0.193$; $p = 0.04$) and positively correlated with ovulation ($r = 0.342$; $p < 0.001$), serum AMH ($r = 0.545$; $p = 0.004$), and luteal phase P4 ($r = 0.251$; $p = 0.009$) (Tab. 3). Clinical pregnancy was negatively correlated with FSH ($r = -0.195$; $p = 0.04$) and positively correlated with luteal phase P4 ($r = 0.296$; $p = 0.002$) (Tab. 4). Although luteal phase P4 was statistically significant in the prediction of ovulation, implantation, and clinical pregnancy, ultrasound verification was not found significant for these parameters (ovulation:

$r = 0.247$; $p = 0.01$; implantation: $r = 0.221$; $p = 0.02$; clinical pregnancy: $r = 0.231$; $p = 0.02$).

DISCUSSION

The success of OI-IUI procedures may be limited by the absence of ovulation detection. In this prospective observational study, ovulation did not occur even with OI treatment in 45.8% of the patients. The association of progesterone measurement and ovarian ultrasound scanning between 72 and 96 hours after hCG treatment can be used to detect ovulation.

According to the present study, P4 levels above 21.3 ng/mL detected successful implantation with 77% sensitivity and 61% specificity, and clinical pregnancy with 90% sensitivity and 61% specificity. In the study by Perkins et al., a P4 threshold level lower than 45 ng/mL was coherent with a nonviable pregnancy in patients treated with assisted reproduction [10]. In the study by Arce et al. [11], mid-luteal P4 levels > 7.9 ng/mL were related to live births during ovulation induction. In accordance with these studies, the progesterone levels seem to be correlated with viable pregnancies both in normal menstrual cycles and ovulation induction cycles. However, there are also conflicting studies. Costello et al., speculated on a forecasting model of mid-luteal P4 levels in patients undergoing OI-IUI and concluded that elevated mid-luteal serum P4 levels were not related to higher pregnancy rates [12]. Yildirim et al. [13] showed a positive relation between luteal phase P4 and

Table 2. Luteal phase progesterone and BMI in predicting ovulation

Predictor	AUC	Cut-off value	Sensitivity (%)	Specificity (%)
LFP	0.739, $p < 0.001$	10.3 ng/mL	98	51
BMI	0.657, $p = 0.005$	23.9 kg/m ²	71	50

AUC — area under the curve; BMI — body mass index; LFP — luteal phase progesterone

Table 3. Correlation values for implantation and other variables

Implantation												
	Age	Gravidity	Parity	BMI	Primary/secondary infertility	FSH	LH	AMH	P on HCG day	Ovulation	LFP	Fetal Cardiac Activity
*r Value	-0.089	0.025	-0.05	-0.192	-0.019	-0.187	0.17	0.332	-0.184	0.339	0.295	0.895
**P value	0.0375	0.808	0.619	0.055	0.854	0.061	0.09	0.113	0.065	0.001	0.03	<0.001

*Correlation coefficient; **The level of statistical significance; AMH — anti-mullerian hormone; BMI — body mass index; FSH, follicle-stimulating hormone; LH — luteinizing hormone; P — progesterone

Table 4. Comparison of the clinical data of the clinical pregnancy group and the group without pregnancy

	CP*(+)			CP (-)			P (MWU**)
	Median	SD	IQR	Median	SD	IQR	
Age [years]	27	4.1	7	28	4.7	7	0.9
BMI [kg/m ²]	22.5	4.2	3.8	25	3.9	4.9	0.08
FSH [mIU/mL]	3.8	2.9	3.9	5.9	2.5	2.5	0.03
AFC	8	4.9	7.8	8	6.1	8.5	0.6
Progesterone 1	6	0.2	0.3	0.8	1.9	0.9	0.1
Progesterone 2	33.4	8.6	14.1	15.5	12.1	16.9	0.001
Endometrial Thickness	13	2.8	3	11	2.6	4	0.1

*CP — Clinical pregnancy; **MWU — Mann-Whitney U; IQR — interquartile range; BMI — body mass index; FSH — follicle-stimulating hormone; SD — standard deviation

clinical pregnancy rates in women with mixed diagnoses, as did Arce et al. [11] in a group of anovulatory women.

Pregnancy rates per OI-IUI cycles in the literature are quite low compared with *in vitro* fertilization (IVF) and favourable scores are usually achieved in 3 consecutive cycles [14]. As it is not known whether ovulation occurs in all OI-IUI cycles, it leads to reduced success, time loss, and increased cost in patients without ovulation despite OI-IUI.

IUI protocols may vary among centres and among practising physicians, even in an individual centre. A luteal phase P4 level is obtained at the initial assessment of the infertile couple; however, routine establishment of P4 levels is not established in each cycle. Follicular development has been evaluated using TVUS, but physicians are not curious to observe the ovulation routinely, either by TVUS or by progesterone measurement in OI-IUI cycles [5]. The hCG trigger is administered according to serial TVUS findings and this is performed at an earlier time than one would expect a follicle to mature in a natural cycle. In patients who received OI-IUI treatment, ovulation was confirmed in only 54.2% by luteal P4 measurement. The P4 threshold was accepted as 10 ng/mL for ovulation to exclude luteal phase defect [9]. In 45.8% of the patients, ovulation was not verified even with ovulation induction treatment. All implantations were in the ovulation detected group with luteal phase P4 > 10 ng/mL. P4 evaluation in the luteal phase is convenient and an inexpensive measurement. By combining it with ultrasound scanning 72–96 hours after the hCG injection day, we can find the optimal treatment for patients with infertility in their next cycle.

The mean BMI of our patients was 25.3 ± 3.9 kg/m². In our ROC analysis model, we calculated that BMI > 23.9 kg/m² was a reliable indicator of anovulation. Similarly, it was shown that obesity was related to lower oocyte retrieval during assisted reproductive technologies, lower clinical pregnancy rates, and higher pregnancy loss phenomenon [15, 16].

A limitation of this study is the inclusion of two different protocols for OI with CC and rFSH. Although both medications work in different physiologies, statistically there is no difference between these treatment groups in terms of ovulation, implantation, and clinical pregnancy rates. Further studies with larger cohorts are needed to prove our results.

CONCLUSIONS

Measuring serum luteal P levels combined with TVUS in IUI cycles can aid in determining success rates. Ovulation detection in OI-IUI cycles may be helpful in planning the next IUI cycle or directing patients directly to IVF.

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Conflict of interest

All authors declare no conflict of interest.

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