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# Measuring the serum progesterone level on the day of transfer can be an additional tool to maximize ongoing pregnancies in single euploid frozen blastocyst transfers

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مرکز تحقیقات بهداشت باروری ولی عصر

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# INTROUDUCTION

- Number of FET procedure has been increasing
- Improvement of COH regimens
- Higher embryo survival rates after vitrification and elective single ET
- Freeze all policies due to prevention of OHSS and detrimental aspect of ovarian stimulation are increasing FET cycles
- **Lower pregnancy rate with low and high serum P levels on day of ET**

- Two study measure P level in ET day in FET cycle

- Serum progesterone <10 ng/ml was observed in 37% of cycles and was associated with significantly lower pregnancy and live birth rates

  (Cedrin-Durnerin et.al )

- OPR significantly lowered between women with serum P < 9.2 ng/ml versus ≥9.2 ng/ml (E. Labarta et. al)

- Aim of this study is to determine whether an optimal P level exists for patients receiving IM administration on the day of FET for a successful outcome in cycles utilizing single euploid blastocysts

# Material & Methods

- Prospective cohort study
- All embryos were artificially hatched on day 3 and biopsied on day 5
- Only  day 5 hatched blastocysts which fully survived after warming  procedure were included
- Exclusion criteria:
  - Uterine diseases (fibroid , polyps , mullerian abnormalities )
  - Hydrosalpinx
  - endometrial thickness <7mm
- Trophoectoderm biopsy was performed : PGT-A , NGS determined  euploid or aneuploid
- Evaluation of viability after warming
- Viability after warming was quantified based on the percentage of intact blastomeres ( 100%,  >50%, 50% ,0% )

# Endometrial preparation

- HRT was used for endometrial preparation
- Estradiol in step –up regimen then ultrasonography and determine ET
- Endometrial thickness < 7  was excluded
- ET >7 mm , start IM progesterone (100 mg per day )
- Serum progesterone level was measured , if > 1 ng/ml ET  was concealed
- ET was performed on $6^{th}$ day of progesterone prescription
- Serum hormonal analysis on $6^{th}$  p administration and 1 hour before ET

# Outcome measurements

- B-hcG positive rate : B-hcG > 5
- Clinical pregnancy rate : Detection of intrauterine GS
- Ongoing pregnancy rate : viable pregnancy on ultrasound beyond 16 W
- Miscarriage rate : Loss of clinical pregnancy before 12 W

## Data collection

168 patients were eligible

- They divided to 2 subgroups according to presence or absence of ongoing pregnancy

- Serum P levels on day ET divided to quartiles ( 0 -25 %, 25 -50 % 50 -75 % , 75 -100% )

- Binary regression analysis for confiding factors

# Result

- B-hcG positive rate 69.6% , Clinical pregnancy rate 64%
- Ongoing pregnancy rate 58.9% , Miscarriage rate 8.3%
- Group I (presence of OP ) vs Group II (Absence of OP ) serum P level on day of ET was significantly higher
- Mean serum P level on day of ET was 32.2+2.3 ng/ml

# Serum P level for each quartile

Clinical outcome according to serum P values (ng/ml) on the day of ET

| Variable | Q1 (< 13.6 ng/ml) (*n* = 42) | Q2 (13.6–24.3 ng/ml) (*n* = 43) | Q3 (24.4–53.2 ng/ml) (*n* = 42) | Q4 (> 53.2 ng/ml) (*n* = 41) | *p*-value |
|---|---|---|---|---|---|
| Female age (years) | 33 (26–43) | 32 (27–44) | 34.5 (23–42) | 31 (28–44) | 0.86 |
| BMI ($kg/m^2$) | 25.1 (20.7–29.6) | 25.1 (17.9–32.8) | 23.3 (18.4–33.5) | 22.3 (18.4–26.4) | 0.211 |
| Clinical Pregnancy Rate n (%) | 15/42 (35.7) | 34/43 (79.1) | 25/42 (59.5) | 34/41 (82.9) | < 0.001* |
| Ongoing Pregnancy Rate n (%) | 11/42 (26.2) | 32/43 (74.4) | 22/42 (52.4) | 34/41 (82.9) | < 0.001* |
| Miscarriage Rate n (%) | 4/15 (26.7) | 2/34 (5.9) | 3/25 (12) | 0/34 (0) | 0.015* |

*statistically significant difference; p < 0.05
Values are given as the median (minimum-maximum) or number (percentage). *p*-values were calculated with Chi-square test and non-parametric independent samples median test
**p* < 0.05 for the following pairwise comparisons: Q1 vs Q2, Q1 vs Q3, Q1vs Q4
** p < 0.05 for the following pairwise comparisons: Q1 vs Q2, Q1 vs Q3, Q1vs Q4
***p < 0,05 for the following pairwise comparisons: Q1 vs Q2, Q1 vs Q4

# logistic regression

- Serum P levels on day of ET was the only significant variable that affect ongoing pregnancy
- Serum P levels on ET day,  has weak negative correlation  with BMI
- Serum P level showed significant predictive value for OPR (Optimal P level: **20.6 ng/ml**)

# Discussion

- P level on ET day in single euploid blastocyst was an independent prognostic factor for OPR
- Serum P level was higher with I.M. progesterone but tissue P level was higher with vaginal progesterone
- Serum P levels on ET day exhibited a wide range
- Serum P level on ET day weakly  negative correlate with BMI
- women with a higher BMI would likely benefit from higher doses of P from the start of administration.
- - Not optimal penetration of the lipophilic progesterone into the muscle
- - A larger volume of distribution
- Serum P levels on the day of ET in fresh donor IVF/ICSI cycles were positively correlated with CPR & LBR (Brady et al. ).

- The effects of serum P concentrations on the endometrial histology and gene expression patterns

- ✓ Morphological delay was observed in the group supplemented with lower P concentrations

- ✓ Higher P levels resulted in normal histology but aberrant gene expression

- Abnormal BCL6 expression in the endometrium of infertile women is associated with endometrial P resistance
- High BCL6 expression is a biomarker for endometrial inflammation
- oestrodiol and P are important components of immune reactions during implantation and pregnancy
- Inflammatory pathway is regulated by certain serum and tissue P levels and P activity

- very low P levels are sufficient to induce histological endometrial maturation, but endometrial histological maturation is not a valid measure of the quality of luteal function or endometrial receptivity

# limitation of the study

- only women with appropriate endometrial thickness and good quality euploid blastocysts were included.

# Conclusion

- The P level on the day of ET is an independent prognostic factor for an ongoing pregnancy.
- The effectiveness of hormonal monitoring immediately before FET has not been proven to be beneficial.
- Determining the threshold levels as well as the dose for the individualization of P treatment may improve the pregnancy outcome.