

RESEARCH

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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

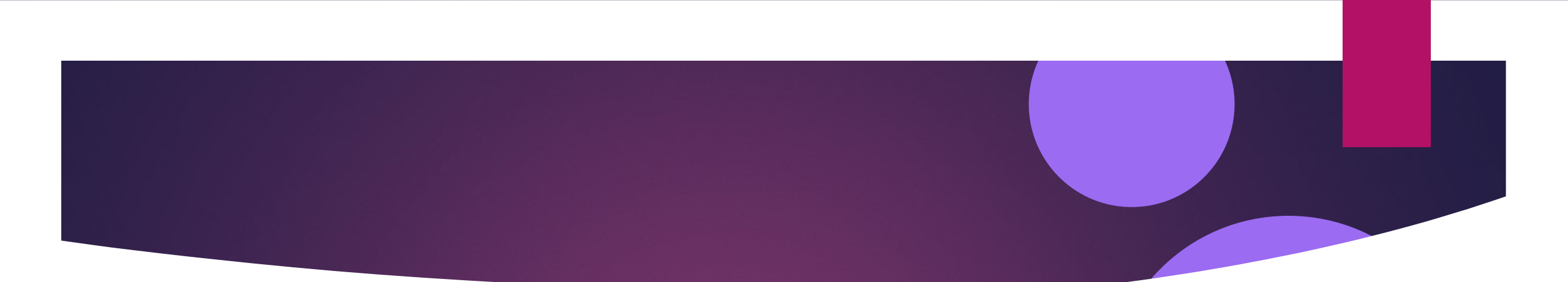
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# INTROUDUCTION

- ❖ 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**

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- ▶ 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  $\geq 9.2$  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<sup>th</sup> day of progesterone prescription
- Serum hormonal analysis on 6<sup>th</sup> p administration and 1 hour before ET

# Outcome measurements

- ❖ B-hcG positive rate :  $B\text{-hcG} > 5$
- ❖ 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  $32.2 \pm 2.3$  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 <sup>2</sup> )	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

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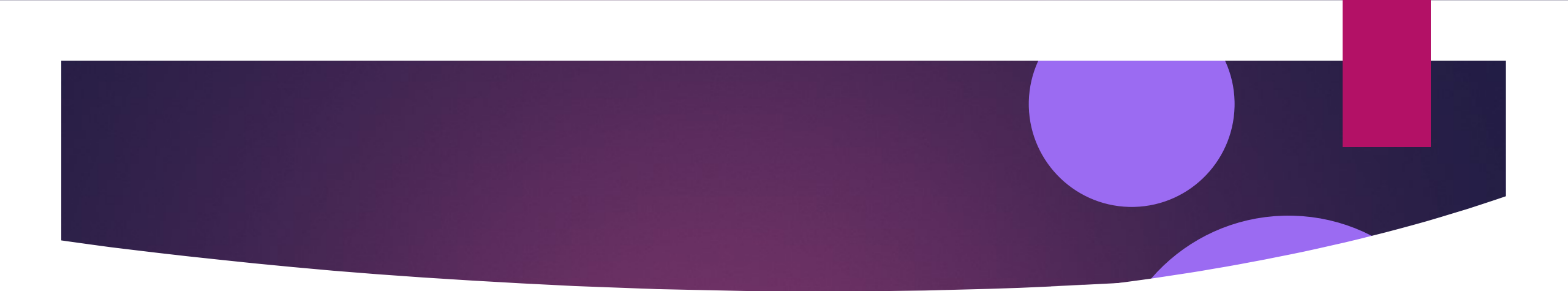
\*\*\* $p < 0,05$  for the following pairwise comparisons: Q1 vs Q2, Q1 vs Q4

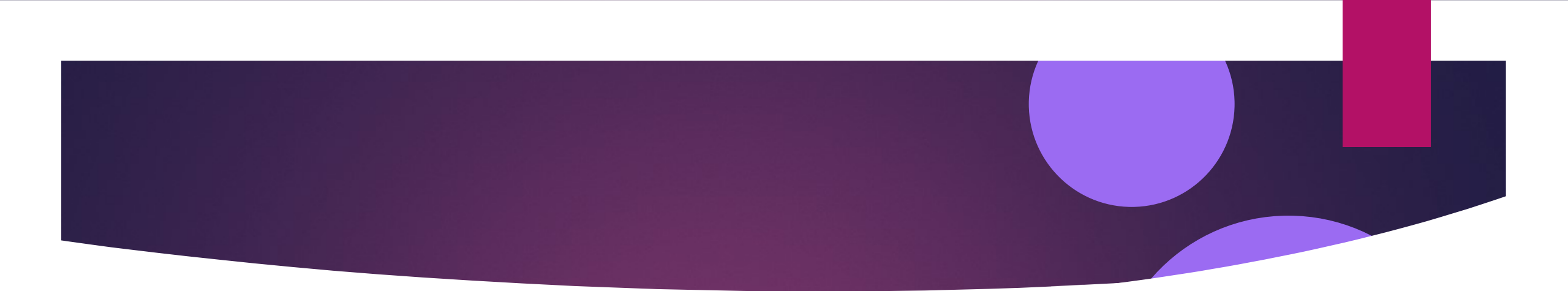
# logistic regression

- ▶ 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. ).

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- ❖ 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

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- 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.