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Title:

MODE OF PROGESTERONE ADMINISTRATION IN EUPLOID, SINGLE EMBRYO TRANSFER CYCLES: IS THERE A HETEROGENEITY OF PATIENT RESPONSE?

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Objective:

Progesterone (P4) plays an integral role in endometrial transformation from the proliferative to the luteal phase prior to embryo transfer. While P4 supplementation is almost universally used, the mode of administration varies from clinic to clinic and even from doctor to doctor. This study aimed to understand patient variables that predict outcome in cycles using intramuscular (IM) progesterone in oil versus combined oral and vaginal progesterone (PO/PV) supplementation.

Design:

Retrospective cohort study

Materials and Methods:

The study included patients who underwent autologous IVF cycles and a subsequent single, euploid embryo FET between 2012 and 2017. Trophectoderm biopsy and pre-implantation genetic testing (PGT) was performed on all embryos. Patients undergoing natural endometrial preparation were excluded. All patients were started on 50mg IM progesterone or a combination of 100mg Endometrin and 200mg Prometrium. Patient age, BMI, gravidity, parity, endometrial thickness and pattern, day of FET, and P4 levels (prior to FET, 2 days following FET (Day+9)

and 9 days after FET (Day+16)) were recorded. Data was analyzed using chi square, fisher's exact test, student's t-test and multivariate logistic regression.

Results:

A total of 1,753 single, euploid FET cycles were performed in which patients underwent IM endometrial preparation (n=1,220) or PO/PV regimen (n=533). BMI, gravidity, parity and day of ET were similar between groups. Patients in the IM group were slightly younger (36.4 vs 36.8, p=0.03), had significantly lower P4 levels prior to transfer (21.9 ± 13.3 vs 31.1 ± 24.1, p<0.0001) and on day+9 (25.0 ± 8.25 vs 31.2 ± 24.0, p<0.0001) and more often had an endometrium in the early secretory phase at time of transfer than the PO/PV group. Bivariate analysis revealed a significantly higher implantation rate and ongoing pregnancy (OP) rate and lower clinical pregnancy loss (CPL) rate among patients on IM versus PO/PV progesterone [Table 1]. After adjusting for possible confounders, the IM group was found to have 1.3 times higher likelihood of OP (95% CI 1.1-1.6) and 40% lower likelihood of CPL (OR 0.6, 95% CI 0.4-0.8) compared to the PO/PV group.

Conclusions:

Analysis of single euploid FET cycles provides a unique opportunity to contribute to the long debated topic of the ideal mode of progesterone supplementation. This study demonstrates heterogeneity in patient response to different progesterone regimens and suggests there might be a subset of patients who have improved pregnancy outcomes with IM supplementation compared to PO/PV. However in an era of personalized medicine, providers must account for patient satisfaction, compliance and response to prescribed regimens. Further research is needed to determine whether progesterone receptor polymorphisms differentially impact endometrial luteinization the likelihood of implantation following FET.

Support:

None

Table 1.

Patient Demographics and Cycle Characteristics based on Method of Progesterone Supplementation

	IM Progesterone (N=1223)	PO/PV Progesterone (N=535)	P Value
Age (y)	36.4 ± 3.84	36.8 ± 3.77	0.03
BMI (kg/m^2)	23.4 ± 4.13	23.3 ± 4.10	NS

Gravidity	1.23 ± 1.48	1.31 ± 1.46	NS
Parity	0.43 ± 0.77	0.46 ± 0.71	NS
Endometrial Thickness at Transfer (mm)	9.63 ± 2.01	9.10 ± 1.72	<0.001
Early Secretory Endometrium at time of transfer	12.8% (156/1223)	9.3% (50/535)	0.04
Day 5 ET	66.1% (808/1223)	65.0% (348/535)	NS
P4 prior to transfer (+5/+6) (ng/mL)	21.9 ± 13.3	31.1 ± 24.1	<0.001
P4 +16 (ng/mL)	25.9 ± 8.70	27.4 ± 18.1	NS
Implantation Rate	770/1223= 63.0%	314/535=58.7%	<0.001
Ongoing Pregnancy Rate	676/1223=55.3%	253/535=47.3%	0.002
Clinical Pregnancy Loss Rate	94/1223=7.7%	61/535=11.4%	0.01