Effect of the follicular phase on pregnancy outcomes in natural frozen embryo transfer cycles

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BACKGROUND

- In programmed FET cycles, prolonged exposure to unopposed estradiol beyond four weeks or a limited exposure of <9 days, even with appropriate endometrial thickness, results in worse pregnancy rates
- It is unknown how follicular phase characteristics affect pregnancy outcomes in natural FET cycles

OBJECTIVE

- Determine whether length of the follicular phase and time of exposure to unopposed estradiol affects pregnancy and live birth outcomes in natural FET cycles

METHODS

- Retrospective cohort study of infertility patients who underwent their first natural FET cycle at our center
- Patients were stratified into two groups based on the cohorts' median cycle day of LH surge: Group 1 (follicular length ≤15 days) and Group 2 (follicular length >15 days)
- Secondarily, patients were stratified into two groups based on the cohorts' median number of days from the estradiol level >100 pg/mL to the LH surge: Group 1 (≤3 days) and Group 2 (>3 days)
- Patients without an estradiol measured between 100-199 pg/mL were excluded from the secondary analysis
- Primary outcome: pregnancy and live birth rates.
- Logistic regression analysis, adjusted *a priori* for patient age, number of embryos transferred, and use of PGT was used to estimate the odds ratio (OR) with a 95% confidence interval (CI)

RESULTS

- The study cohort included 2,358 patients (follicular length ≤15 days: 1,287 patients and follicular length >15 days: 1,071 patients)
- The mean ± SD age was 36.2 ± 4.2 in Group 1 and 35.5 ± 4.3 in Group 2
- On the day of LH surge, Group 1 had a mean estradiol level of 292.2 ± 123.8 pg/mL and mean LH level of 39.4 ± 19.8 mIU/mL, and Group 2 had a mean estradiol level of 294.0 ± 111.0 pg/mL and mean LH level of 44.7 ± 21.8 mIU/mL
- The number of embryos which were PGT euploid was 363 (28.2%) in Group 1 and 420 (39.2%) in Group 2

Table 1: The association between follicular phase length and pregnancy outcomes

	Follicular length ≤15 days N=1,287	Follicular length >15 days N=1,071
Pregnancy	842 (65.4%) 1.00 (Ref)	739 (69.0%) 1.12 (0.94-1.33)
Live birth*	585 (45.5%) 1.00 (Ref)	551 (51.5%) 1.14 (0.97-1.35)
If pregnant:	(n=842)	(n=739)
SAB†	108 (12.8%) 1.00 (Ref)	87 (11.8%) 1.04 (0.77-1.42)
Live birth*	585 (69.5%) 1.00 (Ref)	551 (74.6%) 1.14 (0.91-1.43)

*Live birth: delivery at ≥24 weeks of gestational age
†Spontaneous abortion: failed pregnancy after the observation of at least a gestational sac on ultrasound

RESULTS CONTINUED

Table 2: The association between unopposed estradiol length and pregnancy outcomes

	E2 >100 to surge ≤3 days N=1,052	E2 >100 to surge >3 days N=839
Pregnancy	690 (65.6%) 1.00 (Ref)	595 (70.9%) 1.30 (1.06-1.58)
Live birth*	490 (46.6%) 1.00 (Ref)	436 (52.0%) 1.23 (1.02-1.48)
If pregnant:	(n=690)	(n=595)
SAB†	89 (12.9%) 1.00 (Ref)	65 (10.9%) 0.86 (0.61-1.21)
Live birth*	490 (71.0%) 1.00 (Ref)	436 (73.3%) 1.08 (0.84-1.39)

CONCLUSIONS

- In a natural FET cycle, a prolonged follicular phase does not affect the pregnancy and live birth outcomes
- However, an estradiol level >100 pg/mL for ≤3 days before the LH surge is associated with worse pregnancy and live birth outcomes
- Once a patient achieves a pregnancy, these cycle-level characteristics no longer affect live birth rates
- These observations provide cycle-level characteristics which can be applied during a natural FET cycle to identify cycles which may not be optimal to proceed with embryo transfer
- Physicians should consider the cancellation of a natural FET cycle in which the time from the estradiol level reaching 100 pg/mL to LH surge is ≤3 days