

Higher risk of preeclampsia and pregnancy-induced hypertension with artificial cycle for Frozen-thawed Embryo Transfer compared to ovulatory cycle or fresh transfer following In Vitro Fertilization

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Study question:

Is there an increased risk of preeclampsia after Frozen-thawed Embryo Transfer(FET) compared to In Vitro Fertilization-fresh transfer(IVF-fresh-ET) according to endometrial type of preparation for FET?

Summary answer:

The frequency of preeclampsia and hypertension were significantly higher in the group of artificial cycle (AC-FET) compared to ovulatory cycle (OC-FET) and fresh-ET ($P<0.0001$).

What is known already:

Risks of maternal morbidity are known to be reduced in pregnancies resulting from FET compared to fresh-ET except for the risk of preeclampsia, that was reported to be significantly higher in pregnancies resulting from FET compared to fresh-ET or spontaneous conception. Most recent studies demonstrate an equal live birth rate with either OC-FET or AC-FET preparation. Few studies compared the maternal vascular morbidities with the two hormonal environments that preside over the early stages of embryonic development: OC (major role of the corpus luteum) and AC (prolonged hormone replacement with high doses of estrogen and progesterone).

Study design, size, duration:

We conducted a 2013-2018 French nationwide cohort study comparing maternal vascular morbidities in 3 groups of single pregnancies > 22 weeks of gestation (WG): FET with AC or OC preparation, and IVF (conventional or ICSI)-fresh-ET. Data were extracted from the French National Health System database (>99% of national deliveries) in which all hospitalizations are registered, containing information on patient characteristics, diagnoses and treatments. Records were merged anonymously. Access to the database was legally approved.

Participants/materials, setting, methods:

68 025 deliveries were included: fresh-ET(n=48 152), OC-FET(n=9 500), AC-FET(n=10 373). In OC-FET, a luteal phase support with progesterone was administered for maximum 6 WG if pregnancy. In AC-FET, progesterone was co-administered with estrogen until 12 WG. Embryos were transferred at cleavage or blastocyst stage.

Vascular disorders were recorded if hospitalization for preeclampsia/eclampsia or hypertension (history of hypertension excluded). Maternal characteristics were included in multivariate analysis. Adjusted odds ratios(aOR) and 95% confidence intervals(CI) were estimated.

Main results and the role of chance:

Maternal characteristics: In multivariate analysis, patients in the FET groups were older (33.4 years (std=4.3) vs. 33.2 years (std=4.4) for fresh-ET, respectively, $P<0.0001$), less often primiparous (aOR=0.68[0.66-0.71], $P<0.0001$) or smokers (aOR=0.84[0.75-0.95]) or with premature ovarian insufficiency (POI) (aOR=0.68 [0.58-0.79]), more frequently with polycystic ovaries (PCOS) (aOR=1.25[1.12-1.39]) and comparable for obesity or diabetes.

In FET groups, 52.2% were AC-FET. There was no difference for maternal age, parity, obesity, smoking, history of diabetes between AC and OC-FET. Endometriosis (aOR=1.26[1.16-1.38]), PCOS (aOR=1.79[1.50-2.15]) and POI (aOR=2.0[1.48-2.72]) were more frequent in AC-FET.

Risks of vascular disorders: The rate of preeclampsia (5.3% vs. 2.3% vs. 2.4%, respectively, $P<0.0001$) and hypertension (4.7% vs. 3.4% vs. 3.3%, respectively, $P=0.0002$) was significantly higher in AC-FET *versus* OC-FET and fresh-ET.

In multivariate analysis, the risk of preeclampsia increased with age, primiparity, obesity, diabetes and POI. The risk was higher in AC-FET *versus* OC-FET (aOR=2.42 [2.06-2.85]) and fresh-ET (aOR=2.43[2.2-2.7]), $P<0.00001$. No difference was found between OC-FET and fresh-ET ($P=0.91$). The risk of pregnancy-induced hypertension increased with age >40 , primiparity, smoking, obesity and diabetes and was higher in AC-FET *versus* OC-FET (aOR=1.50[1.29-1.74], $P<0.0001$) and fresh-ET (aOR=1.50[1.35-1.67], $P<0.0001$) and not different between OC-FET and fresh-ET ($P=0.86$).

Limitations, reasons for caution:

While the strength of this study relies in the number and exhaustiveness of subjects analysed, its limitations are its retrospective and register-based nature that did not enable to refine the risk according to details of techniques and treatments in each group.

Wider implications of the findings:

This large nationwide cohort study highlights 2 important information for physicians : i) the possible deleterious role of high supra-physiological and prolonged doses of estrogen-progesterone supplementation on vascular pathologies ii) the protective role of the corpus luteum present in stimulated or spontaneous OC for their prevention.

Trial registration number: -

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