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Full length article

Early pregnancy complications after frozen-thawed embryo transfer in different cycle regimens: A retrospective cohort study

Janna Pape [a,*], Jérémy Levy [b], Michael von Wolff [a]

[a] University Women's Hospital, Department of Endocrinology and Reproductive Medicine, Inselspital, 3010 Bern, Switzerland
[b] FIVNAT statistician, Swiss Society for Reproductive Medicine, 5001 Aarau, Switzerland

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ABSTRACT

Objective: Frozen-thawed embryo transfers (FET) are a key component of assisted reproductive technologies (ART) and various cycle regimens are used worldwide because of insufficient evidence to favour particular transfer schedules. In this study, we investigated the associations between different cycle regimens and early pregnancy complications as well as live birth rates (LBR) per pregnancy after FET.

Study design: We conducted a retrospective cohort study analysing a total of 7342 pregnancies after FET registered in the Swiss IVF Registry from 2014 to 2019. Women were divided into three groups according to the different cycle regimens: Natural Cycles (NC-FET, n = 998), low-dose Stimulation Cycles (SC-FET, n = 984) and Hormone Replacement Cycles (HRC-FET, n = 5360) leading to pregnancy. Outcomes included early pregnancy complications such as bleeding, miscarriages and ectopic pregnancies. Additionally, we evaluated LBR per pregnancy. Incidences were compared using Fisher's exact or Chi-square tests. Mean values were compared using *t*-tests. Multivariate mixed model analysis was performed with early pregnancy complications as outcome.

Results: The incidence of bleeding in the first trimester (NC: 3.5 %, SC: 4.3 %, HRC: 8.4 %; $p < 0.001$) and miscarriage < 12 weeks (NC: 19.0 %, SC: 19.7 %, HRC: 29.1 %; $p < 0.001$) was highest in HRC-FET.

Multivariate analysis revealed almost doubled adjusted odds ratios of bleeding in the first trimester (aOR 1.92; 95 % CI 1.30–2.81) and miscarriage < 12 weeks (aOR 1.82; 95 % CI 1.51–2.19) in HRC-FET vs NC-FET. There were comparable odds ratios in HRC-FET vs SC-FET. No differences were observed in the outcomes between SC-FET and NC-FET.

Highest proportion of LBR per pregnancy (NC: 78.0 %, SC: 77.2 %, HRC: 68.2 %%; $p < 0.001$) was reported in NC-FET.

Conclusions: This is the latest large European register study evaluating early pregnancy complications and LBR per pregnancy after FET between all three different cycle regimens. Miscarriage rate was highest in HRC-FET which can be translated into lower LBR. Therefore, HRC-FET should be avoided and replaced by SC-FET or NC-FET to achieve better pregnancy outcomes.

Introduction

Over the past decade, frozen-thawed embryo transfer (FET) cycles have increased progressively due to improvements in cryopreservation techniques leading to higher live birth rates, fertility preservation and new demands of preimplantation testing [1]. So far, the best individual approach for endometrium preparation in FET cycles is controversial: FET can be performed either in natural cycles (NC-FET), in low-dose stimulation cycles (SC-FET) or in hormone replacement cycles (HRC-FET) [2]. While NC-FET is only applicable in eumenorrhoeic women, SC-FET and HRC-FET can also be administered in cases of irregular cycles, oligomenorrhea or amenorrhea. HRC-FET is convenient in clinical routine, requiring less monitoring and offering greater flexibility in scheduling blastocyst thawing; however, there is growing evidence that HRC-FET increases the risk of hypertensive disorders [3–5].

There are only few studies which analysed both the associations between cycle regimen and early pregnancy complications as well as live birth rates (LBR) per pregnancy after frozen-thawed embryo transfer

Abbreviations: ART, assisted reproductive technologies; FET, frozen-thawed embryo transfers; HRC, hormone replacement cycle; LBR, live birth rates; NC, natural cycle; PCOS, polycystic ovary syndrome; SC, stimulation cycle.

* Corresponding author.
E-mail address: janna.pape@insel.ch (J. Pape).

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(FET). In 2017, a Cochrane analysis did not find sufficient evidence to support the use of a specific cycle regimen in preference to another since there were only four direct comparisons [6]. In 2021, a network *meta*-analysis including 26 RCTs and 113 cohort studies revealed lowest LBR per transfer in HRC-FET compared with other endometrial preparation protocols [7]. Most of the included studies comprised heterogeneous groups of women and differed in the definitions of cycle regimens. Here, the type of ultrasound guidance during transfers was not described despite of clear evidence that ultrasound guidance significantly increases the percentage of ongoing and live birth rates [8,9]. Furthermore, data on low-dose stimulation cycles is scarce; the majority of comparisons were conducted in NC-FET (with or without ovulation trigger) and HRC-FET [10–13].

In view of this conflicting data, we aim to evaluate the incidence of early pregnancy complications and LBR in all three different cycle regimens by excluding the confounders of transfer-conditions in a cohort of already pregnant women.

Materials and methods

Study population

We conducted a retrospective cohort study collecting a total of 7342 pregnancies that were registered in the Swiss ART-Registry from 2014 to 2019. Inclusion criteria were all pregnancies declared by the physician as "clinical pregnancy", i.e. induced abortions were included, and biochemical pregnancies were not included in the analysis. Exclusion criteria were pregnancies without known outcome.

Women were divided into three groups according to the different cycle regimens for endometrial preparation, which were defined as follows:

- NC-FET (n = 998): Natural cycle with or without hCG ovulation trigger.
- SC-FET (n = 984): Women treated with low-dose ovarian stimulation (recombinant and highly purified human menopause gonadotropin with or without gonadotropin-releasing hormone agonist / antagonist) and with or without luteal phase support.
- HRC-FET (n = 5360): Women who received estradiol and progesterone to stimulate endometrial growth and transformation.

Study outcomes

Outcomes included early pregnancy complications, i.e. bleeding in the first trimester, miscarriage < 12 weeks, late miscarriage between 3 and 6 months of pregnancy, ectopic or heterotopic pregnancies. Furthermore, we compared deliveries (including intrauterine deaths) and LBR per pregnancy between the different cycle regimens.

Statistical analysis

Data was analysed by cycle regimens (NC-FET, SC-FET, HRC-FET) for the entire population. Descriptive statistics were used to present patient and cycle characteristics and early pregnancy outcomes. Occurrences in parameters with two categories were compared using a Fisher's exact test, occurrences in parameters with more than two categories were compared using a Chi-square test. Mean values were compared using a *t*-test. Odds ratios for the pregnancy complications given the cycle regimen were calculated. Adjusted odds ratios with pregnancy complications as outcome and cycle regimen, fertilization technique, number of embryos/zygotes transferred, age of mother, polycystic ovary syndrome (PCOS) and chronic anovulation as fixed effects and centre ID as random effect were also calculated.

None of the p-values generated for the analysis was corrected for multiple testing; p-values are therefore nominal and need to be interpreted accordingly. A p-value < 0.05 was considered to be statistically significant. All analyses were performed with SAS 9.4.

Ethical considerations

Each of the 29 Swiss ART centres was informed about the use of the health-related personal data collected in the registry and gave consent for this research project. The local ethics board approved the protocol (Project-ID: 2021–01671).

Results

Patient characteristics

The mean maternal age was 35.5, 35.6 and 35.3 years in the NC-FET, SC-FET and HRC-FET group respectively. The proportion of previous recurrent miscarriages was overall low (NC: 0.3 %, SC: 0.3 %, HRC: 0.8 %; p = 0.062). The FET groups differed significantly in the proportion of chronic anovulation / PCOS and endometriosis: Lowest rate of chronic anovulation / PCOS (5.7 %) and highest rate of mild endometriosis (8.1 %) were observed in NC-FET. By contrast, chronic anovulation / PCOS (17.6 %) and severe endometriosis (5.7 %) were more present in HRC-FET. Except for thyroid disease (NC: 3.4 %, SC: 3.2 %, HRC: 6.2 %; p < 0.001), there were no significant differences in other clinically relevant comorbidities (Table 1).

Outcomes

Pregnancy outcomes revealed highest incidence of early pregnancy bleeding in HRC-FET (8.4 %) compared to NC-FET (3.5 %) and SC-FET (4.3 %). There were comparable results in the incidence of miscarriage < 12 weeks (NC: 19.0 %, SC: 19.7 %, HRC: 29.1 %; p < 0.001) and no differences in late miscarriages or ectopic pregnancies between the cycle regimens. Highest LBR per pregnancy (78 %) and proportion of singleton deliveries (70.5 %) were achieved in NC-FET (Table 2).

Multivariate analysis revealed>2-fold adjusted odds ratios of bleeding in the first trimester in HRC-FET compared to NC-FET (aOR 1.92; 95 % CI 1.30–2.81) and SC-FET (aOR 2.09; 95 % CI 1.34–3.24). The odds ratios of miscarriage < 12 weeks were approximately doubled in HRC-FET compared to NC-FET (aOR 1.82; 95 % CI 1.51–2.19) and SC-FET (aOR 2.06; 95 % CI 1.67–2.54). NC-FET and SC-FET revealed comparable odds (Table 3).

Discussion

Main findings

This study supports adverse early pregnancy outcomes in cycles in which the corpus luteum is suppressed. We found the highest incidence of early pregnancy bleeding, revealed the highest miscarriage rate < 12 weeks and added the lowest LBR per pregnancy in HRC-FET compared to NC-FET or SC-FET as further important findings (Table 2, 3).

Strengths and limitations

The great strength of our study is the large cohort of pregnancies (n = 7342) after FET in three different cycle regimens, representing the total Swiss ART data during 2014 – 2019. We only included pregnant women in our cohort, thereby excluding potential confounding factors for higher pregnancy rates such as endometrium thickness, its receptivity and synchronization to the embryo [14] as well as hormonal conditions [15–16].

The use of the Swiss ART data registry is both one strength as well as the main limitation of our analysis: studies based on registry data are often accompanied by selection bias (nonrandomized) and missing data (lack of documentation). Potential confounders such as BMI, history of hypertension or preeclampsia [17–18] and laboratory parameters

Table 1
Maternal characteristics in pregnancies after FET by cycle regimen.

Characteristics	NC-FET (n = 998)	SC-FET (n = 984)	HRC-FET (n = 5360)	p-value
Maternal age (years), mean (SD)	35.5 (3.9)	35.6 (4.0)	35.3 (4.1)	**0.007**
Recurrent miscarriage > 2 (%)	3 (0.3)	3 (0.3)	44 (0.8)	0.062
Cause of infertility, n (%)				
Chronic anovulation / PCOS	57 (5.7)	96 (9.8)	945 (17.6)	**<0.001**
Tubal factor	125 (12.5)	145 (14.7)	730 (13.6)	0.356
Uterine malformation	5 (0.5)	13 (1.3)	59 (1.1)	0.126
Uterine fibroids	8 (0.8)	17 (1.7)	73 (1.4)	0.184
Endometriosis (I/II)	81 (8.1)	53 (5.4)	399 (7.4)	**0.034**
Endometriosis (III/IV)	37 (3.7)	34 (3.5)	306 (5.7)	**0.001**
Hypergonadotropic ovarian insufficiency (WHO III)	12 (1.2)	7 (0.7)	99 (1.9)	**0.015**
Hypogonadotropic ovarian insufficiency (WHO I)	1 (0.1)	3 (0.3)	58 (1.1)	**<0.001**
Other female pathologies, n (%)	57 (5.7)	140 (14.2)	603 (11.3)	**<0.001**
Co-morbidities, n (%)				
Diabetes mellitus I/II	1 (0.1)	2 (0.2)	7 (0.1)	0.769
Thyroid disease	34 (3.4)	31 (3.2)	330 (6.2)	**<0.001**
Breast cancer	3 (0.3)	1 (0.1)	7 (0.1)	0.367
Malignancy of the genital tract	0 (0)	0 (0)	9 (0.2)	0.326
Treatment type, n (%)				
IVF	170 (17.0)	202 (20.5)	892 (16.6)	**<0.001**
ICSI	773 (77.5)	411 (41.8)	4247 (79.2)	
Mixed	55 (5.5)	371 (37.7)	221 (4.1)	
Number of embryos / zygotes transferred, n (%)				
1	487 (48.8)	380 (38.6)	2992 (55.8)	**<0.001**
2	483 (48.4)	536 (54.5)	2249 (42.0)	
3	28 (2.8)	68 (6.9)	119 (2.2)	
Number of gestational sacs at beginning of pregnancy, n (%)				
0	37 (3.7)	23 (2.3)	254 (4.7)	**<0.001**
1	857 (85.9)	812 (82.5)	4511 (84.2)	
2	101 (10.1)	143 (14.5)	515 (9.6)	
3	1 (0.1)	4 (0.4)	12 (0.2)	
>3	0 (0)	0 (0)	1 (0)	
Unknown	2 (0.2)	2 (0.2)	67 (1.3)	

FET = frozen-thawed embryo transfers; NC = natural cycle, SC = low-dose stimulation cycle, HRC = hormone replacement cycle.
Occurrences for parameters with two categories were compared using a Fisher's exact test. Occurrences for parameters with more than two categories were compared using a Chi-square test. Mean values were compared using a *t*-test. None of the p-values was corrected for multiple testing.

including vitamin D status [19–20] were not documented and could not be considered while analysing the data. Additionally, different endometrial preparation protocols within specific protocols were not registered and may affect outcomes. Furthermore, PGT data was not available for the analysis period, as PGT was not legally permitted in Switzerland before the end of 2017 and was subsequently slowly introduced over the following years. Selection bias was observed in the

Table 2
Early pregnancy outcome and delivery rates after FET by cycle regimen.

Pregnancy Outcome (%)	NC-FET (n = 998)	SC-FET (n = 984)	HRC-FET (n = 5360)	p-value
Bleeding 1. trimester	35 (3.5)	42 (4.3)	452 (8.4)	**<0.001**
Early miscarriage (<12 weeks)	190 (19.0)	194 (19.7)	1557 (29.1)	**<0.001**
Late miscarriage (3–6 months)	8 (0.8)	6 (0.6)	37 (0.7)	0.897
Ectopic pregnancy	16 (1.6)	8 (0.8)	56 (1.0)	0.203
Heterotopic pregnancy	0 (0)	1 (0.1)	0 (0)	0.134
Induced abortions	5 (0.5)	16 (1.6)	48 (0.9)	0.037
Delivery (incl. intrauterine death) (%)				
No birth	219 (21.9)	224 (22.8)	1699 (31.7)	**<0.001**
Singletons	704 (70.5)	663 (67.4)	3278 (61.2)	
Twins	73 (7.3)	96 (9.8)	375 (7.0)	
Triplets	2 (0.2)	1 (0.1)	8 (0.2)	
Live birth / pregnancy (%)	778 (78.0)	760 (77.2)	3655 (68.2)	**<0.001**

FET = frozen-thawed embryo transfers; NC = natural cycle, SC = low-dose stimulation cycle, HRC = hormone replacement cycle.
Occurrences for parameters with two categories were compared using a Fisher's exact test. Occurrences for parameters with more than two categories were compared using a Chi-square test. None of the p-values was corrected for multiple testing.

form of unequally distributed maternal characteristics and in treatment type (Table 1). The proportion of chronic anovulation / PCOS (17.6 %), severe endometriosis (5.7 %) and thyroid disease (6.2 %) were highest in the HRC-FET group. It has been shown that PCOS is a risk factor for miscarriage in both obese and non-obese women [21], whereas only adenomyosis seems to be associated with miscarriage [22–24]. Thyroid disease might also negatively influence early pregnancy outcomes [25]. However, HRC-FET was applied in a far higher proportion (73 %), implying that most normoovulatory, healthy women also received HRC-FET for practical reasons.

Interpretation

The reasons for better early pregnancy outcomes and higher LBR per pregnancy may lie in the physiological preparation of the endometrium in cycles in which the corpus luteum is not suppressed. So far, it remains unclear whether hormonal substitution in HRC-FET harms embryo development. Supraphysiological hormone levels during early trophoblast invasion might lead to abnormal pregnancy. Excess estradiol levels in the early stage of pregnancy can have adverse effects on placentation, causing cell death and inhibiting trophoblast invasion in cytotrophoblast and placental cell lines [26]. Furthermore, exogenous hormones may lead to thromboembolic events which could impede implantation and cause miscarriage [26–27]. It is presumed that the corpus luteum in NC-FET and SC-FET produces circulating vasoactive hormones such as relaxin and vascular endothelial growth factor [28–30] which reduces the risk of hypertensive disorders in later stages of pregnancy [3–5].

Previous studies have found conflicting results in pregnancy outcomes between the different cycle regimens. In terms of pregnancy rates, they seem to be equally effective [6,31–32]. In terms of LBR per cycle, the largest multi-centre RCT (ANTARCTICA trial) reported comparable LBR in NC-FET compared to HRC-FET; however, more cycles were cancelled in HRC-FET with a dropout rate of > 10 % and the overall success rate was low and miscarriage rate high [33]. The latest Cochrane review [32] stated insufficient evidence on the use of any particular intervention for endometrial preparation. The main limitations in the evidence were poor reporting of study methods and lack of precision in pregnancy outcomes.

Prospective multi-centre randomized control trials with standard

Table 3
Early pregnancy complications after FET by cycle regimen.

Outcome	HRC-FET vs NC-FET			HRC-FET vs SC-FET			SC-FET vs NC-FET		
	Crude OR (95 % CI)	Adjusted OR (95 % CI)	p-value	Crude OR (95 % CI)	Adjusted OR (95 % CI)	p-value	Crude OR (95 % CI)	Adjusted OR (95 % CI)	p-value
Bleeding 1st trimester	2.53 (1.78–3.60)	1.92 (1.30–2.81)	**<0.001**	2.07 (1.49–2.86)	2.09 (1.34–3.24)	**<0.001**	1.23 (0.78–1.94)	0.92 (0.53–1.59)	0.761
Early miscarriage (<12 weeks)	1.74 (1.47–2.06)	1.82 (1.51–2.19)	**<0.001**	1.67 (1.41–1.97)	2.06 (1.67–2.54)	**<0.001**	1.04 (0.84–1.30)	0.88 (0.68–1.15)	0.355
Late miscarriage (3–6 months)	0.86 (0.40–1.85)	0.88 (0.40–1.94)	0.753	1.13 (0.48–2.69)	1.41 (0.53–3.78)	0.492	0.76 (0.26–2.20)	0.62 (0.20–1.98)	0.424
Ectopic pregnancy	0.65 (0.37–1.13)	N/A		1.29 (0.61–2.71)	N/A		0.50 (0.21–1.18)	N/A	
Heterotopic pregnancy	N/A	N/A		N/A	N/A		N/A	N/A	

FET = frozen-thawed embryo transfers; N/A = not applicable, NC = natural cycle, SC = low-dose stimulation cycle, HRC = hormone replacement cycle. Adjusted OR were corrected for cycle regimen, fertilization technique, number of embryos/zygotes transferred, age of mother, chronic anovulation or polycystic ovary syndrome and centre ID. None of the p-values was corrected for multiple testing.

endometrial preparation protocols and definitions are required to determine the best method of endometrial preparation for optimal pregnancy outcomes. Besides the emotional implications of bleeding and miscarriages, interventions such as curettage might lead to intrauterine infection or adhesion which could, in turn, have a negative impact on further embryo transfers. With regard to the high incidence of early pregnancy complications and, moreover, lower LBR per pregnancy in HRC-FET, clinicians should prefer cycle regimens in which the corpus luteum is not suppressed.

Conclusion

This is the latest large European register study evaluating early pregnancy complications and LBR per pregnancy after FET between all three cycle regimens. Miscarriage rate was higher in HRC-FET which could be translated into lower LBR. Thus, NC-FET or SC-FET should be preferred if medically possible. Further research is necessary to clarify the potential mechanism underlying the influence of FET regimens with or without corpus luteum affecting early pregnancy complications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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