Accepted: 17 October 2022

DOI: 10.1111/1471-0528.17343

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

Hormone replacement cycles are associated with a higher risk of hypertensive disorders: Retrospective cohort study in singleton and twin pregnancies

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Funding information
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Abstract

Objective: To elaborate the associations of different cycle regimens (natural cycle [NC], stimulated cycle [SC], hormone replacement cycle [HRC]) on maternal and neonatal adverse pregnancy outcomes after frozen–thawed embryo transfers (FET).

Design: Population-based registry study.

Setting: Swiss IVF Registry.

Population or Sample: Singleton ($n = 4636$) and twin ($n = 544$) live births after NC-FET ($n = 776$), SC-FET ($n = 758$) or HRC-FET ($n = 3646$) registered from 2014 to 2019.

Methods: Fifteen pregnancy pathologies were modelled for singleton and twin pregnancies using mixed models adjusted for cycle regimen, delivery, fertilisation technique, chronic anovulation, age of mother and centre.

Main outcome measures: Maternal (vaginal bleeding, isolated arterial hypertension and pre-eclampsia) and neonatal (gestational age, birthweight, mode of delivery) adverse pregnancy outcomes.

Results: In singleton pregnancies, the incidences of bleeding in first trimester, isolated hypertension and pre-eclampsia were highest in HRC-FET with doubled odds of bleeding in first trimester (adjusted odds ratio [aOR] 2.23; 95% CI 1.33–3.75), isolated hypertension (aOR 2.50; 95% CI 1.02–6.12) and pre-eclampsia (aOR 2.16; 95% CI 1.13–4.12) in HRC-FET vs. NC-FET and with doubled respectively sixfold odds of bleeding (aOR 2.08; 95% CI 1.03–4.21) and pre-eclampsia (6.02; 95% CI 1.38–26.24) in HRC-FET versus SC-FET. In twin pregnancies, the incidence of pre-eclampsia was highest in HRC-FET with numerically higher odds of pre-eclampsia in HRC-FET versus NC-FET and versus SC-FET.

Conclusions: Our data implied the highest maternal risks of hypertensive disorders in HRC-FET, therefore clinicians should prefer SC-FET or NC-FET if medically possible.

KEYWORDS
cycle regimen, frozen–thawed embryo transfer, hypertensive disorder, pre-eclampsia, twin pregnancy

1 | INTRODUCTION

Frozen–thawed embryo transfers (FET) are a key component of assisted reproductive technologies (ART)[1,2] and have increased markedly to 27% of all cycles in Europe.[3–5] Various cycle regimens are used worldwide because of insufficient evidence to favour particular transfer schedules.[6] In general, FET can be performed in Hormone Replacement Cycles (HRC-FET), low-dose Stimulation Cycles (SC-FET) or Natural Cycles (NC-FET).[7] HRC-FET is medically necessary in amenorrhea or irregular cycles. SC-FET can also be applied in irregular cycles; however, it is less frequently used because daily and expensive gonadotrophin injections are required. Practically, HRC-FET offers greater flexibility in scheduling blastocyst thawing, which may be beneficial for both the patient and the in vitro fertilisation clinic.

No differences between these cycle regimens have been demonstrated in terms of pregnancy rates.[6] However, serious maternal and neonatal complications associated with HRC-FET were first described in data from Sweden,[8] Japan[9] and China.[10] A doubled to tripled risk of pre-eclampsia,[8–10] a six-fold risk of placenta accreta[9,11] and doubled risk of caesarean section[11] occurred in HRC-FET compared with NC-FET. A recent systematic review and meta-analysis revealed the lowest risks of hypertensive disorders in pregnancy (relative risk [RR] 0.61, 95% CI 0.50–0.73) and pre-eclampsia (RR 0.47, 95% CI 0.42–0.53) in NC-FET compared with HRC-FET.[12] Data for SC-FET were comparable to those of NC-FET, showing no increased adverse maternal or neonatal outcomes.[8,13]

The inhibition of follicles and luteal bodies,[14,15] altered progesterone[16,17] and supraphysiological estrogen levels[18] in HRC-FET cycles may lead to the above-mentioned pregnancy complications. An insufficient cardiovascular adaptation was observed in women without corpus luteum,[19] which may be caused by the lack of circulating vasoactive hormones released by the corpus luteum.[20]

So far, most register studies have been conducted in singleton pregnancies and data are also poor for SC-FET. Regarding the increasing rate of HRC-FET cycles worldwide, it is essential to elaborate the associations of each cycle regimen with maternal and neonatal adverse pregnancy outcomes, not only in singletons but also in in twin pregnancies.

2 | METHODS

2.1 | Study population

We conducted a retrospective cohort study collecting singleton and twin births after FET that were registered in the Swiss ART Registry from 2014 to 2019. The inclusion criterion was live birth after FET. Exclusion criterion was stillbirth.

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

- NC-FET: Natural cycle with or without human chorionic gonadotrophin ovulation trigger
- SC-FET: Women treated with low-dose ovarian stimulation (recombinant and human menopausal gonadotrophin with or without gonadotrophin-releasing hormone agonist/antagonist) and with or without luteal phase support
- HRC-FET: Women who received estradiol and progesterone to stimulate endometrial growth and transformation.

2.2 | Outcomes

Maternal outcomes included pregnancy complications, e.g. bleeding in first, second and third trimester, premature labour, premature rupture of membranes, placenta praevia, isolated hypertension (>140/90 mmHg), pre-eclampsia, intrauterine growth restriction and gestational diabetes.

Neonatal outcomes comprised gestational age with pre- and post-term births, weight at birth with the proportion of small and large for gestational age and mode of delivery.

2.3 | Statistical analysis

Data were analysed by cycle regimens (NC-FET, SC-FET, HRC-FET) for the entire population or in singleton and twin pregnancies. Descriptive statistics were used to present patient and cycle characteristics, and maternal and neonatal outcomes. Adjusted odds ratios with pregnancy complications as outcome and cycle regimen, fertilisation technique, age of mother, polycystic ovary syndrome (PCOS) and chronic anovulation as fixed effects and subcentre ID ($n = 71$) as random effect were also calculated.

None of the p values generated for the analysis were corrected for multiple testing; the p values are therefore nominal and need to be interpreted accordingly. All analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA.

3 | RESULTS

Our study cohort comprised a total of 4636 singleton and 544 twin births (corresponding to 1088 twins), which were distributed into the three groups: NC-FET ($n = 776$), SC-FET ($n = 758$) and HRC-FET ($n = 3646$).

The mean maternal ages were 35.3, 35.3 and 35.1 years in the NC-FET, SC-FET and HRC-FET groups, respectively. The proportion of previous recurrent miscarriages was overall low (NC: 0.3%, SC: 0.3%, HRC: 0.7%). The FET groups differed in the proportion of chronic anovulation or PCOS (NC: 5.9%, SC: 10.0%, HRC: 17.3%) and severe endometriosis (NC: 3.6%, SC: 3.8%, HRC: 5.8%). Except for thyroid disease (NC: 3.6%, SC: 3.4%, HRC: 5.8%), there were no differences in comorbidities. The largest proportion of single embryo transfers were conducted in HRC-FET (56.0%) and double embryo transfers in SC-FET (55.0%). Numbers of triple embryo transfers were overall low with the highest rate in SC-FET (7.0%). Day of embryo transfer (day 2/3 or day 5) was not documented in the registry. Maternal characteristics separated into singleton and twin deliveries were comparable (Table 1).

3.1 | Singleton pregnancies

Differences between the cycle regimens with highest incidences in HRC-FET were observed in bleeding in the first trimester (NC: 2.8%, SC: 2.6%, HRC: 7.0%), premature rupture of membranes (NC: 1.4%, SC: 1.4%, HRC: 3.1%), isolated hypertension (NC: 0.9%, SC: 0.2%, HRC: 1.8%) and pre-eclampsia (NC: 1.7%, SC: 0.3%, HRC: 2.8%) (Table 2).

TABLE 1 Maternal characteristics in frozen embryo transfers (FET) by cycle regimen

Characteristics	Singleton deliveries (n = 4636)				Twin deliveries (n = 544)			
	NC-FET (n = 703)	SC-FET (n = 662)	HRC-FET (n = 3271)	p value	NC-FET (n = 73)	SC-FET (n = 96)	HRC-FET (n = 375)	p value
Maternal age (years), mean (SD)	35.4 (3.9)	35.5 (3.9)	35.2 (4.0)	0.064	34.6 (3.8)	33.8 (4.0)	34.0 (4.3)	0.516
Recurrent miscarriage >2, *n* (%)	2 (0.3)	2 (0.3)	25 (0.8)	0.257	0	0	1 (0.3)	1.000
Cause of infertility, *n* (%)								
Chronic anovulation/PCOS	42 (6.0)	70 (10.6)	546 (16.7)	*<0.001*	4 (5.5)	6 (6.3)	84 (22.4)	*<0.001*
Tubal factor	88 (12.5)	107 (16.2)	455 (13.9)	0.147	7 (9.6)	12 (12.5)	45 (12.0)	0.858
Uterine malformation	4 (0.6)	6 (0.9)	34 (1.0)	0.555	1 (1.4)	1 (1.0)	0	0.096
Uterine fibroids	3 (0.4)	13 (2.0)	40 (1.2)	*0.029*	0	2 (2.1)	1 (0.3)	0.131
Endometriosis (I/II)	55 (7.8)	32 (4.8)	244 (7.5)	*0.035*	6 (8.2)	9 (9.4)	21 (5.6)	0.318
Endometriosis (III/IV)	25 (3.6)	27 (4.1)	193 (5.9)	*0.013*	3 (4.1)	2 (2.1)	17 (4.5)	0.626
Hypergonadotropic ovarian insufficiency (WHO III)	12 (1.7)	6 (0.9)	59 (1.8)	0.260	0	0	4 (1.1)	1.000
Hypogonadotropic ovarian insufficiency (WHO I)	1 (0.1)	2 (0.3)	31 (0.95)	*0.029*	0	0	4 (1.1)	1.000
Other female pathologies	35 (5.0)	94 (14.2)	345 (10.5)	*<0.001*	3 (4.1)	12 (12.5)	35 (9.3)	0.171
Comorbidities, *n* (%)								
Diabetes mellitus I/II	1 (0.1)	2 (0.3)	4 (0.1)	0.330	0	0	2 (0.5)	1.000
Thyroid disease	25 (3.6)	24 (3.6)	187 (5.7)	*0.010*	3 (4.1)	2 (2.1)	25 (6.7)	0.214
Breast cancer	3 (0.4)	1 (0.2)	6 (0.2)	0.360	0	0	0	
Malignancy of the genital tract	0	0	7 (0.2)	0.586	0	0	1 (0.3)	1.000
Treatment type, *n* (%)								
IVF	121 (17.2)	136 (20.5)	538 (16.4)	*<0.001*	9 (12.3)	26 (27.1)	62 (16.5)	*<0.001*
ICSI	547 (77.8)	292 (44.1)	2616 (80.0)		59 (80.8)	30 (31.3)	296 (78.9)	
Mixed	35 (5.0)	234 (35.4)	117 (3.6)		5 (6.8)	40 (41.7)	17 (4.5)	
Number of embryos/zygotes transferred, *n* (%)								
1	376 (53.5)	286 (43.2)	2015 (61.6)	*<0.001*	7 (9.6)	2 (2.1)	27 (7.2)	0.083
2	315 (44.8)	332 (50.2)	1205 (36.8)		63 (86.3)	85 (88.5)	332 (88.5)	
3	12 (1.7)	44 (6.6)	51 (1.6)		3 (4.1)	9 (9.4)	16 (4.3)	

Italic values indicate significance of $p < 0.05$.

In SC-FET, gestational diabetes occurred most frequently (NC: 4.6%, SC: 6.9%, HRC: 4.5%) and intrauterine growth restriction least frequently (NC: 1.8%, SC: 0.2%, HRC: 1.3%). There were no differences in the incidences of bleeding in the second and third trimesters, premature labour in the second trimester, placenta praevia, cervical insufficiency with cerclage, hospitalisation in pregnancy and cholestasis between cycle regimens. The registry choice 'other pregnancy complications' was different between the groups and lowest in HRC-FET (NC: 47.9%, SC: 42.0%, HRC: 28.5%) (Table 2).

Multivariate analysis revealed doubled odds of bleeding in the first trimester (adjusted odds ratio [aOR] 2.23; 95% CI 1.33–3.75), isolated hypertension (aOR 2.50; 95% CI 1.02–6.12) and pre-eclampsia (aOR 2.16; 95% CI 1.13–4.12) in HRC-FET compared with NC-FET. There were doubled odds of bleeding in the first trimester (aOR 2.08; 95% CI 1.03–4.21) and even six-fold odds of pre-eclampsia in HRC-FET compared with SC-FET (aOR 6.02; 95% CI 1.38–26.24). The odds of developing gestational diabetes were lower in HRC-FET (aOR 0.51; 95% CI 0.30–0.88) compared with SC-FET. NC-FET and SC-FET revealed comparable odds in most cases (Table 2).

Overall, neonatal outcomes including gestational age, the proportion of pre- and post-term births and birthweight were similar in the three FET groups. Differences were shown in the mode of delivery: highest caesarean section rates were reported in HRC-FET (NC: 38.4%, SC: 44.3%, HRC: 51%) and highest spontaneous birth rates in NC-FET (NC: 51.2%, SC: 45.0%, HRC: 33.8%) (Table 3).

3.2 | Twin pregnancies

Pre-eclampsia showed a difference between the cycle regimens with the highest incidence in HRC-FET (NC: 2.7%, SC: 1.0%, HRC: 7.2%). Similar to singleton pregnancies, intrauterine growth restriction occurred least frequently in SC-FET (NC: 8.2%, SC: 0%, HRC: 2.9%). There were no relevant

TABLE 2 Pregnancy outcome of singletons ($n = 4636$) in frozen embryo transfers (FET) by cycle regimen

Outcomes	Deliveries ($n = 4636$)			Multivariate analysis					
	Incidence (%)			HRC-FET vs. NC-FET		HRC-FET vs. SC-FET		SC-FET vs. NC-FET	
Pregnancy pathology (%)	NC-FET ($n = 703$), n (%)	SC-FET ($n = 662$), n (%)	HRC-FET ($n = 3271$), n (%)	Adjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Bleeding in first trimester	20 (2.8)	17 (2.6)	230 (7.0)	2.23 (1.33–3.75)	*0.003*	2.08 (1.03–4.21)	0.042	1.07 (0.47–2.45)	0.870
Bleeding in second trimester	5 (0.7)	6 (0.9)	39 (1.2)	2.09 (0.77–5.69)	0.150	1.42 (0.46–4.40)	0.543	1.47 (0.35–6.11)	0.596
Bleeding in third trimester	9 (1.3)	6 (0.9)	24 (0.7)	0.55 (0.23–1.30)	0.173	1.18 (0.38–3.65)	0.779	0.46 (0.13–1.61)	0.227
Premature labour in second trimester	6 (0.9)	1 (0.2)	28 (0.9)	n.a.	–	n.a.	–	n.a.	–
Premature labour in third trimester	11 (1.6)	2 (0.3)	37 (1.1)	n.a.	–	n.a.	–	n.a.	–
Premature rupture of membranes	10 (1.4)	9 (1.4)	101 (3.1)	1.20 (0.56–2.54)	0.643	1.07 (0.40–2.82)	0.898	1.12 (0.36–3.52)	0.845
Placenta praevia	8 (1.1)	6 (0.9)	32 (1.0)	0.94 (0.40–2.22)	0.888	1.30 (0.43–3.93)	0.647	0.73 (0.20–2.60)	0.622
Isolated hypertension >140/90 mmHg	6 (0.9)	1 (0.2)	60 (1.8)	2.50 (1.02–6.12)	*0.045*	1.30 (0.43–3.93)	0.647	0.38 (0.04–3.48)	0.391
Pre-eclampsia	12 (1.7)	2 (0.3)	93 (2.8)	2.16 (1.13–4.12)	*0.019*	6.02 (1.38–26.24)	*0.017*	0.36 (0.07–1.74)	0.203
Eclampsia	2 (0.3)	9 (1.4)	5 (0.2)	n.a.	–	n.a.	–	n.a.	–
Intrauterine growth restriction	13 (1.8)	1 (0.2)	42 (1.3)	n.a.	–	n.a.	–	n.a.	–
Gestational diabetes	32 (4.6)	46 (6.9)	147 (4.5)	0.96 (0.61–1.52)	0.873	0.51 (0.30–0.88)	*0.016*	1.88 (0.99–3.57)	0.053
Cervical insufficiency with cerclage	1 (0.1)	5 (0.8)	8 (0.2)	1.93 (0.22–17.03)	0.554	0.52 (0.12–2.21)	0.374	3.73 (0.34–41.35)	0.283
Hospitalisation in pregnancy	15 (2.1)	24 (3.6)	97 (3.0)	1.62 (0.88–2.97)	0.119	1.26 (0.65–2.44)	0.497	1.29 (0.57–2.93)	0.545
Cholestasis	1 (0.1)	0 (0)	8 (0.2)	n.a.	–	n.a.	–	n.a.	–
Unknown	0	1 (0.2)	4 (0.1)	n.a.	–	n.a.	–	n.a.	–
Other	337 (47.9)	278 (42.0)	931 (28.5)	0.39 (0.32–0.48)	*<0.001*	0.24 (0.18–2.19)	*<0.001*	1.60 (1.18–2.19)	*0.003*

Italic values indicate significance of $p < 0.05$.

TABLE 3 Neonatal outcome of singletons and twins in frozen embryo transfers (FET) by cycle regimen

	Singleton deliveries ($n = 4636$)				Twin deliveries ($n = 544$)			
Neonatal outcome	**NC-FET ($n = 703$)**	**SC-FET ($n = 662$)**	**HRC-FET ($n = 3271$)**	***p* value**	**NC-FET ($n = 73$)**	**SC-FET ($n = 96$)**	**HRC-FET ($n = 375$)**	***p* value**
Gestational age, *n* (%)								
Mean, weeks (wk) (SD)	38.8 (1.9)	38.6 (3.1)	38.7 (2.3)	0.141	35.8 (2.3)	35.3 (3.2)	35.3 (3.6)	0.552
Post-term >42 weeks	3 (0.4)	4 (0.6)	19 (0.6)	0.745	0 (0)	0 (0)	2 (0.5)	0.260
≥37 to <42 weeks	626 (89.0)	581 (87.8)	2909 (88.9)		27 (37.0)	25 (26.0)	119 (31.7)	
≥32 to <37 weeks	64 (9.1)	63 (9.5)	291 (8.9)		43 (58.9)	65 (67.7)	214 (57.1)	
≥28 to <32 weeks	8 (1.1)	6 (0.9)	27 (0.8)		1 (1.4)	2 (2.1)	26 (6.9)	
<28 weeks	2 (0.3)	8 (1.2)	25 (0.8)		2 (2.7)	4 (4.2)	14 (3.7)	
Delivery mode, *n* (%)								
Spontaneous	360 (51.2)	298 (45.0)	1104 (33.8)	*<0.001*	8 (11.0)	11 (11.5)	51 (13.6)	0.405
Forceps	11 (1.6)	25 (3.8)	69 (2.1)		0 (0)	0 (0)	4 (1.1)	
Vacuum	57 (8.1)	20 (3.0)	388 (11.9)		2 (2.7)	0 (0)	13 (3.5)	
Caesarean section	270 (38.4)	293 (44.3)	1668 (51.0)		63 (86.3)	83 (86.5)	301 (80.3)	
Unknown/Missing	5 (0.7)	26 (3.9)	42 (1.3)		0	2 (2.1)	6 (1.6)	
Neonate 1: Birthweight, *n* (%)								
Mean, g (SD)	3324.4 (523.3)	3316.6 (579.2)	3357.4 (559.3)	0.118	2477.5 (523.7)	2437.2 (566.1)	2440.5 (616.9)	0.881
≥4000 g	63 (9.0)	66 (10.0)	324 (9.9)	0.680	0 (0)	0 (0)	0 (0)	0.969
≥2500 to <4000 g	602 (85.6)	555 (83.8)	2771 (84.7)		38 (52.1)	52 (54.2)	195 (52.0)	
≥1500–2500 g	32 (4.6)	28 (4.2)	127 (3.9)	0.072	31 (42.5)	37 (38.5)	151 (40.3)	0.837
<1500 g	6 (0.9)	12 (1.8)	40 (1.2)		4 (5.5)	6 (6.3)	27 (7.2)	
Unknown/Missing (g)	0 (0)	1 (0.2)	9 (0.3)		0 (0)	1 (1)	2 (0.5)	
Normal range, centile	557 (79.2)	548 (82.8)	2637 (80.6)		60 (82.2)	75 (78.1)	293 (78.1)	
SGA (<10th centile)	94 (13.4)	60 (9.1)	338 (10.3)		7 (9.6)	12 (12.5)	37 (9.9)	
LGA (>90th centile)	49 (7.0)	50 (7.6)	269 (8.2)		6 (8.2)	7 (7.3)	38 (10.1)	
Unknown/Missing (centile)	3 (0.4)	4 (0.6)	27 (0.8)		0 (0)	2 (2.1)	7 (1.9)	
Neonate 2: Birthweight, *n* (%)								
Mean, g (SD)					2410.3 (535.9)	2388.6 (616.6)	2382.0 (605.1)	0.934
≥4000 g					0 (0)	1 (1.0)	0 (0)	0.469
≥2500to <4000 g	n.a.				35 (48.0)	43 (44.8)	181 (48.3)	
≥1500–2500 g					33 (45.2)	44 (45.8)	158 (42.1)	
<1500 g					5 (6.9)	7 (7.3)	33 (8.8)	
Unknown/Missing (g)					0 (0)	1 (1.0)	3 (0.8)	

(Continues)

TABLE 3 (Continued)

	Singleton deliveries ($n = 4636$)				Twin deliveries ($n = 544$)			
Neonatal outcome	**NC-FET ($n = 703$)**	**SC-FET ($n = 662$)**	**HRC-FET ($n = 3271$)**	***p* value**	**NC-FET ($n = 73$)**	**SC-FET ($n = 96$)**	**HRC-FET ($n = 375$)**	***p* value**
Normal range, centile					57 (78.1)	73 (76.0)	284 (75.7)	
SGA (<10th centile)					11 (15.1)	13 (13.5)	50 (13.3)	0.981
LGA (>90th centile)					5 (6.9)	8 (8.3)	33 (8.8)	
Unknown/Missing (centile)					0 (0)	2 (2.1)	8 (2.1)	

Italic value indicate significance of $p < 0.05$.

differences in any other incidences of pregnancy outcomes by cycle regimens (Table 4).

Multivariate analysis showed numerically higher odds for pregnancy complications in HRC-FET. The odds of pre-eclampsia doubled compared with NC-FET (aOR 2.54; 95% CI 0.54–11.94) and multiplied compared with SC-FET (aOR 4.05; 95% CI 0.47–34.74), and the odds of bleeding in the first trimester increased five-fold in HRC-FET compared with SC-FET (aOR 5.52; 95% CI 0.54–56.43) (Table 4).

Similar to singletons, there were no differences in neonatal outcomes, but twins were mainly born by caesarean section in all cycle regimens (NC: 86.3%, SC: 86.5%, HRC: 80.3%).

4 | DISCUSSION

This study shows an association between hypertensive disorders and HRC-FET. We found the highest incidences of bleeding in the first trimester, isolated hypertension and pre-eclampsia in singleton pregnancies. To our knowledge, this is the first study to investigate the associations of pregnancy outcomes among different cycle regimens also in a large cohort of SC-FET and twin pregnancies.

Previous studies have found that HRC-FET is an important risk factor for hypertensive disorders.[8,9,21–23] Conflicting results are described in neonatal outcomes including lack of statistical differences between cycle regimen,[24] but also higher proportions of post-term deliveries,[11] macrosomia[8] and large-for-gestational-age babies[25–27] in HRC-FET. These divergent outcomes may be explained by different sample sizes or various baseline characteristics of the cohorts, especially in the percentage of women with PCOS.

Our cohort revealed a high proportion of HRC-FET both in singleton (70.6%) and twin pregnancies (68.9%), which is comparable to Japan (72%)[9] and far higher compared with Sweden (15%)[8] and Denmark (31%).[23] These register studies mainly analysed singleton deliveries[8,13,22,23,28] or restricted the sensitivity analysis to singletons.[11] Furthermore, the majority of studies compared HRC-FET with NC-FET[9,22,28] and cycle regimens were defined differently. The Swedish study[8] defined SC-FET as natural cycles with ovulation trigger. The Danish study[23] separated the groups into natural cycles with (= modified NC-FET) or without (= true NC-FET) an ovulation trigger. In our study, SC-FET comprised all methods of low-dose ovarian stimulation and NC-FET was defined by lack of ovarian stimulation.

In our analysis, we not only confirmed the higher risk profile in FET regimens without corpus luteum showing increased risks of hypertensive disorders but additionally added the following findings:

In singleton pregnancies, bleeding in the first trimester occurred more often in NC-FET and multivariate analysis revealed doubled odds in HRC-FET compared with NC-FET. Excess estradiol levels in the early stage of pregnancy have been shown to have adverse effects on placentation, causing cell death, inhibiting trophoblast invasion

TABLE 4 Pregnancy outcome of twins ($n = 544$) in frozen embryo transfers (FET) by cycle regimen

Outcomes	Deliveries ($n = 544$)			Multivariate analysis					
	Incidences (%)			HRC-FET vs. NC-FET		HRC-FET vs. SC-FET		SC-FET vs. NC-FET	
Pregnancy pathology (%)	NC-FET ($n = 703$), n (%)	SC-FET ($n = 662$), n (%)	HRC-FET ($n = 3271$), n (%)	Adjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Bleeding in first trimester	3 (4.1)	1 (1.0)	20 (5.3)	1.62 (0.40–6.50)	0.497	5.52 (0.54–56.43)	0.149	0.29 (0.02–3.89)	0.351
Bleeding in second trimester	2 (2.7)	1 (1.0)	9 (2.4)	0.92 (0.18–4.61)	0.918	5.92 (0.63–55.81)	0.120	0.16 (0.01–1.99)	0.152
Bleeding in third trimester	1 (1.4)	3 (3.1)	7 (1.9)	1.39 (0.16–11.80)	0.765	0.97 (0.18–5.16)	0.976	1.42 (0.12–16.40)	0.777
Premature labour in second trimester	1 (1.4)	0	13 (3.5)	n.a.	–	n.a.	–	n.a.	–
Premature labour in third trimester	8 (11.0)	4 (4.2)	33 (8.8)	n.a.	–	n.a.	–	n.a.	–
Premature rupture of membranes	4 (5.5)	7 (7.3)	30 (8.0)	1.64 (0.53–5.05)	0.386	0.85 (0.31–2.30)	0.745	1.94 (0.48–7.80)	0.351
Placenta praevia	0 (0)	0 (0)	3 (0.8)	n.a.	–	n.a.	–	n.a.	–
Isolated hypertension >140/90 mmHg	0 (0)	0 (0)	7 (1.9)	n.a.	–	n.a.	–	n.a.	–
Pre-eclampsia	2 (2.7)	1 (1.0)	27 (7.2)	2.54 (0.54–11.94)	0.238	4.05 (0.47–34.74)	0.201	0.63 (0.05–8.18)	0.721
Eclampsia	0 (0)	6 (6.3)	3 (0.8)	n.a.	–	n.a.	–	n.a.	–
Intrauterine growth restriction	6 (8.2)	0 (0)	11 (2.9)	n.a.	–	n.a.	–	n.a.	–
Gestational diabetes	4 (5.5)	5 (5.2)	18 (4.8)	0.89 (0.26–2.99)	0.845	1.31 (0.35–4.87)	0.685	0.68 (0.14–3.35)	0.630
Cervical insufficiency with cerclage	0 (0)	0 (0)	3 (0.8)	n.a.	–	n.a.	–	n.a.	–
Hospitalisation in pregnancy	9 (12.3)	13 (13.5)	48 (12.8)	1.76 (0.73–4.28)	0.208	0.96 (0.37–2.44)	0.925	1.85 (0.56–6.05)	0.311
Cholestasis	1 (1.4)	0 (0)	6 (1.6)	n.a.	–	n.a.	–	n.a.	–
Unknown	0 (0)	0 (0)	2 (0.5)	n.a.	–	n.a.	–	n.a.	–
Other	34 (46.6)	38 (39.6)	136 (36.3)	0.44 (0.24–0.80)	0.007	0.52 (0.28–0.95)	0.033	0.85 (0.39–1.83)	0.670

in cytotrophoblast and placental cell lines,[29] which might be reflected by frequent bleeding. Gestational diabetes occurred more often in SC-FET compared with HRC-FET. Decreased secretion of insulin-counteracting hormones from the placenta is discussed as suppressing the pathogenesis of gestational diabetes in some HRC-FET-derived pregnancies.[9,30]

In twin pregnancies, the incidence of pre-eclampsia was also highest in HRC-FET in the multivariate analysis (Table 4); however, the overall low absolute numbers of complications might explain this statistical result.

Regarding neonatal outcomes, we found the highest caesarean section rate in HRC-FET and the highest spontaneous birth rate in NC-FET. The higher percentage of pregnancy complications might be one important reason for the higher proportion of caesarean sections in HRC-FET. Twins are usually delivered by caesarean section because of inherent higher obstetric risks, which could explain the lack of differences between the cycle regimens (Table 3).

4.1 | Strengths and limitations

The great strength of our study is the large cohort of singleton (n = 4636) and twin (n = 544) pregnancies after three different cycle regimens, representing the total Swiss ART data of the years 2014–19. The use of the Swiss ART data registry is both a strength and the main limitation of our analysis. Studies based on registry data are often accompanied by selection bias (nonrandomised) and missing data (lack of documentation). The data are observational in nature and it is possible that treatment patterns (unmeasured confounders) might be responsible for the observed associations. Furthermore, with the large number of outcomes, some observed associations might have occurred by chance and might not reflect an existing relationship. In the current analysis, selection bias occurred in unequally distributed maternal characteristics such as PCOS and in treatment type (Table 1). Additionally, undocumented, background characteristics might have had an impact on the clinician's choice of treatment method. Potential confounders like body mass index (BMI), history of hypertension or pre-eclampsia[31,32] were not documented and could not be considered while analysing the data. As a result of the positive correlation between PCOS and BMI, it is possible that the HRC-FET group comprised a larger proportion of women with higher BMI. However, the relative proportion of PCOS women in HRC-FET was small overall (17.3%) and cannot explain the far higher application of HRC-FET cycles (70.4%) and therefore the pregnancy complications. It can be assumed that most normo-ovulatory women also received HRC-FET for practical reasons. Moreover, we were able to adjust for PCOS in the multivariate analysis.

The data also shows a large number of pregnancies with 'other pregnancy complications'. A supportive analysis was conducted excluding centres with more than 40% of 'other' or less than 10% of specified pregnancy complications. As the results on maternal and neonatal outcomes were comparable in this approach, a bias by inaccurate documentation could be excluded.

Some studies also question whether pre-implantation genetic testing (PGT) for aneuploidy may increase the risk of pre-eclampsia or gestational hypertension.[33,34] PGT became legally permitted in Switzerland at the end of 2017 and was slowly introduced during the following years. Therefore, no PGT data are available for the analysis period.

Additionally, a quantification of blood loss and/or bleeding episodes would have been interesting to analyse but were not documented in the registry. This aspect should be investigated in prospective cohort studies.

5 | CONCLUSION

This is the first large register study to demonstrate an association between the three different cycle regimens including a large proportion of SC-FET and twin pregnancies.

Our data showed higher odds of bleeding, isolated hypertension and pre-eclampsia in patients conceiving after HRC-FET compared with NC-FET and SC-FET, indicating that these risks might be associated with the inhibition of the luteal body development. In twin pregnancies, the incidence of pre-eclampsia was also higher. Prospective randomised controlled trials[35] are essential to clarify the potential mechanism underlying the influence of FET regimens with or without corpus luteum affecting pregnancy complications.

AUTHOR CONTRIBUTIONS

All authors met conditions for authorship. JP interpreted the data, drafted the first version of the article and revised the manuscript. JL provided critical inputs on the study design, performed statistical analyses and revised the manuscript. MvW conceptualised the study, interpreted the data and revised the manuscript. All authors edited and approved the final version for publication.

ACKNOWLEDGEMENTS

We thank all 29 Swiss ART centres who gave consent for this research project. We thank the Institut Biochimique SA, Lugano for financial support and Dr Elizabeth Krämer for linguistic revision.

FUNDING INFORMATION

Statistical calculation was financially supported by IBSA Institut Biochimique SA, which did not have any role in designing or conducting the study and the calculations, nor in the decision on preparation or publication of the manuscript.

CONFLICT OF INTERESTS

JL received payment for statistical analysis and revision of the manuscript (payment by MvW). JP and MvW: none declared. Completed disclosure of interests form available to view online as supporting information.

BJOG An International Journal of Obstetrics and Gynaecology

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

ETHICS APPROVAL

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).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pape J, Levy J, von Wolff M. Hormone replacement cycles are associated with a higher risk of hypertensive disorders: Retrospective cohort study in singleton and twin pregnancies. BJOG. 2022;00:1–10. https://doi.org/10.1111/1471-0528.17343