

## GYNECOLOGY

# Neonatal and maternal outcome after frozen embryo transfer: Increased risks in programmed cycles



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**BACKGROUND:** Frozen embryo transfer is associated with better perinatal outcome regarding preterm birth and low birthweight, yet higher risk of large for gestational age and macrosomia compared to fresh transfer. Further, higher rates of hypertensive disorders in pregnancy are noted after frozen embryo transfer. Whether these differences are due to the protocol used in frozen cycles remains unknown.

**OBJECTIVE:** To analyze the obstetric outcome after frozen embryo transfer depending on protocol used. Comparison was also made for frozen vs fresh transfer and for frozen transfer vs spontaneous conception.

**STUDY DESIGN:** A population-based retrospective registry study including all singletons born after frozen embryo transfer in Sweden from 2005 to 2015. The in vitro fertilization register was cross-linked with the Medical Birth Register, the Register of Birth Defects, the National Patient Register, the Swedish Neonatal Quality Register, and the Prescribed Drug Register. Singletons after frozen embryo transfer were compared depending on the presence of a corpus luteum in the actual cycle. All frozen transfer singletons were also compared with fresh transfer and spontaneous conception singletons. Primary outcomes were preterm birth (<37 w), low birthweight (<2500 g), hypertensive disorders in pregnancy, and postpartum hemorrhage (>1000 mL). Crude and adjusted odds ratio with 95% confidence interval were calculated and adjustment made for relevant confounders.

**RESULTS:** A total of 9726 singletons were born after frozen embryo transfer (natural cycles, n = 6297; stimulated cycles, n = 1983; programmed cycles, n = 1446), 24,365 after fresh transfer, and 1,127,566 after spontaneous conception. No significant differences were noticed for preterm birth and low birthweight between the different protocols used in

frozen embryo transfer. Compared to natural and stimulated frozen cycles, programmed frozen cycles were associated with a higher risk of hypertensive disorders in pregnancy (adjusted odds ratio, 1.78; 95% confidence interval, 1.43–2.21 and adjusted odds ratio, 1.61; 95% confidence interval, 1.22–2.10, respectively) and postpartum hemorrhage (adjusted odds ratio, 2.63; 95% confidence interval, 2.20–3.13 and adjusted odds ratio, 2.87; 95% confidence interval, 2.29–2.60, respectively). Moreover, higher risks for postterm birth (adjusted odds ratio, 1.59; 95% confidence interval, 1.27–2.01 and adjusted odds ratio, 1.98; 95% confidence interval, 1.47–2.68) and macrosomia (adjusted odds ratio, 1.62; 95% confidence interval, 1.26–2.09 and adjusted odds ratio, 1.40; 95% confidence interval, 1.03–1.90) were detected. There were no significant differences in any outcomes between stimulated and natural cycles. Frozen cycles in general compared to fresh cycles and compared to spontaneous conceptions showed neonatal and maternal outcomes in agreement with earlier studies.

**CONCLUSION:** No significant difference could be seen regarding preterm birth and low birthweight between the different protocols. However, higher rates of hypertensive disorders in pregnancy, postpartum hemorrhage, postterm birth, and macrosomia were detected in programmed cycles. Stimulated cycles had outcomes similar to natural cycles. These findings are important in view of the increasing use of frozen cycles and the new policy of freeze-all cycles in in vitro fertilization. The results suggest a link between the absence of corpus luteum and adverse obstetric outcomes.

**Key words:** Frozen embryo transfer, obstetric outcome, low birthweight, macrosomia, hypertensive disorders in pregnancy, postpartum bleedings

In Europe, the rate of frozen embryo transfer (FET) has steadily been rising and in several countries FET accounted for approximately 40% of all in vitro fertilization (IVF) cycles in 2015.<sup>1</sup> In the United States the rate of FET has doubled since 2005, being 30% of nondonor assisted reproductive therapy (ART) in 2015.<sup>2</sup> A new trend, the

freeze-all strategy, has shown promising results with preserved<sup>3–5</sup> or even higher<sup>6</sup> live birth rates and decreased incidence of ovarian hyperstimulation syndrome.

Singletons born after FET have better neonatal outcomes compared to singletons born after fresh embryo transfer regarding low birthweight (LBW), small for gestational age (SGA), and preterm birth (PTB) but worse neonatal outcomes compared to singletons born after spontaneous conception.<sup>7–9</sup> However, children born after FET are at a greater risk of being born as large for gestational age (LGA) and macrosomic (>4500 g) compared to both fresh cycles and spontaneous conception.<sup>7–10</sup> Further, higher rates of hypertensive disorders in

pregnancy (HDP) are noted in FET cycles, both compared to fresh IVF cycles and compared to spontaneous conception<sup>7,8,11,12</sup> The reasons behind these findings are not known.

Earlier studies have shown similar results regarding implantation rates, clinical pregnancy rates, or live birth rates when comparing different protocols in FET,<sup>13,14</sup> while few studies have investigated the neonatal and maternal outcomes comparing these strategies. Recent studies suggest a link between the presence or absence of corpus luteum (CL) in FET cycles and preeclampsia.<sup>15–17</sup> Higher rates of preeclampsia were noted in programmed FET cycles, where no CL is present,

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## AJOG at a Glance

**Why was this study conducted?**

Since an increasing number of in vitro fertilization cycles are performed as frozen embryo transfer, including the freeze-all strategy, we aimed to analyze the obstetric outcome after frozen embryo transfer depending on protocol used. Recent studies have shown a link between the absence of corpus luteum and a higher risk of preeclampsia.

**Key findings**

No significant difference could be found regarding preterm birth and low birthweight. However, higher rates of hypertensive disorders in pregnancy, postpartum hemorrhage, postterm birth, and macrosomia were detected in programmed cycles.

**What does this add to what is known?**

The results support the hypothesis of a link between absence of corpus luteum in programmed cycles and adverse maternal outcomes. This is important information because an increasing number of in vitro fertilization cycles worldwide are performed as frozen embryo transfer and should encourage use of natural cycles.

compared to FET cycles using protocols where 1 or more CL occur.

The aim of this study was to compare neonatal and maternal outcome for singletons after cryopreservation of embryos, replaced in programmed cycles (no CL), stimulated cycles (at least 1 CL), or natural cycles (1 CL), adjusting for relevant confounders. A comparison was also made between singletons from frozen and fresh cycles as well as between singletons from frozen cycles and spontaneous conception (SC).

**Materials and Methods****Study design**

The present study is a population-based registry study in Sweden including all IVF singleton deliveries from autologous oocytes during the years 2005–2015 grouped into FET in programmed, stimulated, or natural cycles and fresh embryo transfer. Using the unique personal identification number, allocated to every citizen in Sweden, we cross-linked data on deliveries from the Medical Birth Register/IVF (MBR/IVF) and the National Register of Assisted Reproduction (Q-IVF)<sup>18</sup> with the following registers: the Swedish Medical Birth Register (MBR), the Register of Birth Defects, the National Patient Register (NPR), the Swedish Neonatal Quality Register, and the Prescribed Drug Register. Through 2006, data on all ART treatments resulting in a

delivery were reported to the National Board of Health and Welfare and stored at MBR, thus named MBR/IVF. After 2007, treatment characteristics and results from all Swedish IVF clinics, both public and private, are to be reported to the Q-IVF. Data derived from the IVF registries included information about treatment (fresh or frozen-thawed transfer), number of oocytes received, fertilization method (IVF or intracytoplasmic sperm injection), freezing method (vitrification or slow-freeze), culture duration, date of embryo transfer, number of embryos transferred, number of gestational sacs, and date of delivery. The MBR provided data on maternal characteristics (ie, age, parity, body mass index, smoking habits, years of involuntary childlessness) and data on delivery and neonatal outcomes. The MBR, established in 1973, covers almost all deliveries in Sweden and has been found to have high validity.<sup>19–21</sup> The Register of Birth Defects and NPR supplied information on birth defects during the infant's first year of life and the NPR also provided information on cause of infertility according to the International Classification of Diseases (ICD)-10 codes. Neonatal diagnoses were obtained from the Swedish Neonatal Quality Register according to ICD-10 codes. Since detailed data on medication during the ART treatment are not available in the IVF registers, data on the medication used

during IVF treatment were extracted from the Prescribed Drug Register using the following anatomic therapeutic chemical codes: G03CA03 (estrogen); G03DA04 (progesterone); G03GA01 to G03GA06, G03GA08, and G03GA10 (gonadotropin); G03GB01 to G03GB03 (clomiphene citrate); L02AE01 (buserelin); L02AE04 (triptorelin); L02BG04 (letrozole); H01CA (nafarelin); and H01CC (ganirelix, cetrorelix). All medication mentioned above, purchased within 70 days prior to embryo transfer, was considered as belonging to the actual nonnatural FET cycle and grouped into subgroups according to the anatomic therapeutic chemical codes and treatment regimens ([Appendix: Supplementary Tables 1–3](#)). Cycles were grouped according to presence or absence of a CL. The first group included natural cycles performed without any exogenous hormones and based on the endogenous luteinizing hormone surge (1 CL). The second group, stimulated cycles, was a mix of cycles using different ovulatory agents (modified natural cycles including human chorionic gonadotropin [hCG] trigger, ovulation induction including clomiphene citrate or letrozole with or without hCG, gonadotropin stimulation including follicle stimulating hormone or human menopausal gonadotropin with or without gonadotropin-releasing hormone agonist/antagonist, or luteal support including progesterone with or without hCG) (at least 1 CL). The third group, programmed cycles, included estrogen and progesterone with or without suppression with a gonadotropin-releasing hormone agonist/antagonist (no CL). All cycles using any kind of drug were named nonnatural cycles.

Information about paternal age at birth and parental education level was obtained from the central authority for recording statistics on all Swedish citizens, Statistics Sweden.<sup>22</sup>

Data on deliveries included all live births and stillbirths. Before July 1, 2008, stillbirths  $\geq 28$  completed gestational weeks and from July 1, 2008, stillbirths  $\geq 22$  completed gestational weeks were included, in accordance with the change in definition of stillbirth in Sweden.

Comparisons were made between singleton pregnancies after FET in programmed cycles, singletons in stimulated cycles, and singleton pregnancies after FET in natural cycles. Comparisons were also made between singleton pregnancies following FET and singleton pregnancies following fresh embryo transfer as well as for singleton pregnancies following SC.

## Outcomes

The primary outcomes were PTB (<37 weeks), LBW (<2500 g), HDP (pregnancy-induced hypertension [ICD-10 code O13] and preeclampsia [ICD-10 code O14-O15]), and postpartum hemorrhage (PPH) (ICD-10 code O72; >1000 mL). Other neonatal outcomes included postterm birth ( $\geq 42$  weeks), very and extreme PTB (<32 weeks, <28 weeks, respectively), very LBW (<1500 g), SGA (<2 standard deviations [SD] below the Swedish growth standard, adjusted for gestational age and sex),<sup>23</sup> LGA (>2 SD above the Swedish growth standard, adjusted for gestational age and infant sex),<sup>23</sup> fetal macrosomia (>4500 g), Apgar score <7 at 5 minutes, perinatal mortality (stillbirth and death in the first week of life) and neonatal mortality (death <28 days postpartum), neonatal morbidity related to PTB (retinopathy of prematurity, bronchopulmonary dysplasia, intraventricular hemorrhage grade 3, and necrotizing enterocolitis), and major birth defects according to the EUROCAT classification.<sup>24</sup>

Gestational age was determined from the second-trimester ultrasonography for the majority of SC pregnancies, or from the first day of the last menstrual period if information from ultrasonography was missing. In IVF pregnancies gestational age was determined according to the day of embryo transfer and the number of days in culture.

Other maternal outcomes included placenta previa (ICD-10 code O44) and placental abruption (ICD-10 code O45). The rate of cesarean section was also assessed.

## Statistical analysis

Descriptive statistics are given by number (n) and percentages for categorical

variables and by mean and SD for continuous variables. Multivariable logistic regression was performed and adjustments made for maternal age, body mass index, parity, year of birth of child, maternal smoking, chronic hypertension, child's sex, level of maternal education, and years of involuntary childlessness. For comparison between ART pregnancies, adjustment was also made for cause of infertility, IVF/intracytoplasmic sperm injection, culture duration, and number of gestational sacs. For programmed and stimulated vs natural cycles, adjustment was moreover made for freezing method (vitrification or slow-freeze). Crude and adjusted odds ratios (AOR) with 95% confidence intervals (CI) for each outcome were calculated. The cause of infertility was hierarchically arranged in order for patients to have only 1 cause of infertility, and infertility more likely to affect the perinatal outcomes was put higher in the hierarchy.<sup>25,26</sup> The order of hierarchy was anovulation/polycystic ovary syndrome (PCOS), tubal factors, endometriosis, unexplained infertility, male factor infertility, and other female factors. A 95% CI not including 1 was defined as statistically significant. Analyses were conducted using SPSS version 24.0 (IBM Corp, Armonk, NY) and STATA version 15 (StataCorp, College Station, TX).

## Post hoc power calculation

With 6297 and 1446 singletons conceived after natural and programmed FET, respectively, it was possible to detect a difference in PTB <37 weeks and HDP of 2.1%, from 6.0% to 8.1%. ( $\alpha = 0.05$ ,  $\beta = 0.80$ ).

## Ethics

Permission for this study was given from the Regional Ethical Committee at the University of Gothenburg (Dnr 304/06, T109-08, T087-12 and Dnr 214-12, T422-12, T516-15, T233-16, T300-17, T1144-17, T121-18).

## Results

During the study period, 9726 singletons were born following FET: 6297 in natural cycles, 1983 in stimulated cycles, and 1446 in programmed cycles. There were

24,365 singletons born following fresh embryo transfer and 1,127,566 following SC. Demographic data are presented in Table 1 and, regarding subgroups for nonnatural cycles, in Supplementary Table 1.

Neonatal outcomes are summarized in Tables 2 and 4 and, regarding subgroups for nonnatural cycles, in Supplementary Table 2. Maternal outcomes are summarized in Tables 3 and 5 and, regarding subgroups for stimulated cycles, in Supplementary Table 3. Neonatal and maternal outcomes following FET and compared to fresh cycles and SC are presented in Supplementary Table 4 (Appendix).

## Neonatal outcomes

### Programmed vs natural and stimulated frozen embryo transfer

No significant difference could be found regarding PTB (<37 weeks), LBW (<2500 g), or LGA between the groups. However, programmed FET was associated with an increased risk of macrosomia (AOR, 1.62; 95% CI, 1.26–2.09) and postterm birth (AOR, 1.59; 95% CI, 1.27–2.01) compared to natural FET as well as compared to stimulated cycles (AOR, 1.40; 95% CI, 1.03–1.90, and AOR, 1.98; 95% CI, 1.47–2.68, respectively) (Table 4). In a 00000 comparison of stimulated cycles with natural cycles, no significant difference was found.

Results of subgroups of nonnatural FET cycles are shown in Supplementary Table 2.

### Frozen embryo transfer vs fresh in vitro fertilization

FET was associated with decreased risks of PTB (<37 weeks) (AOR, 0.80; 95% CI, 0.72–0.89), LBW (<2500 g) (AOR, 0.66; 95% CI, 0.57–0.75), very LBW (<1500 g) (AOR, 0.70; 95% CI, 0.51–0.96), and SGA (AOR, 0.63; 95% CI, 0.55–0.73) compared to fresh IVF. It was also associated with higher risks of postterm birth (AOR, 1.58; 95% CI, 1.41–1.77), LGA (AOR, 1.62; 95% CI, 1.44–1.82), macrosomia (AOR, 1.93; 95% CI, 1.69–2.21), Apgar score <7 at 5 minutes (AOR, 1.28; 95% CI, 1.10–1.48), and meconium aspiration

TABLE 1

**Maternal characteristics of singleton pregnancies after frozen embryo transfer (natural, stimulated, and programmed cycles), fresh embryo transfer, and spontaneous conception in Sweden, 2005–2015**

Outcome	All FET	FET, natural cycles	FET, stimulated cycles	FET, programmed cycles	Fresh embryo transfer	Spontaneous conception
Deliveries, n	9726	6297	1983	1446	24,365	1,127,566
Year of birth, n (%)						
2005–2008	2166 (22.3)	1542 (24.5)	268 (13.5)	356 (24.6)	7407 (30.4)	393,117 (34.9)
2009–2011	2761 (28.4)	1755 (27.9)	588 (29.7)	418 (28.9)	7231 (29.7)	312,345 (27.7)
2012–2015	4799 (49.3)	3000 (47.6)	1127 (56.8)	672 (46.5)	9727 (39.9)	422,104 (37.4)
Maternal age, mean $\pm$ SD	34.9 $\pm$ 5.2	34.9 $\pm$ 4.1	35.2 $\pm$ 4.2	34.3 $\pm$ 4.3	34.1 $\pm$ 4.3	30.7 $\pm$ 5.2
Maternal age (years), n (%)						
$\leq$ 34	4343 (44.7)	2781 (44.2)	814 (41.0)	748 (51.7)	12,584 (51.6)	856,678 (76.0)
35–37	2261 (23.2)	1474 (23.4)	476 (24.0)	311 (21.5)	5288 (21.7)	140,450 (12.5)
38–39	1412 (14.5)	957 (15.2)	284 (14.3)	171 (11.8)	3047 (12.5)	60,411 (5.4)
$\geq$ 40	1355 (13.9)	842 (13.4)	340 (17.1)	173 (12.0)	2633 (10.8)	53,037 (4.7)
Missing	355 (3.7)	243 (3.9)	69 (3.5)	43 (3.0)	813 (3.3)	16,990 (1.5)
Paternal age, mean $\pm$ SD	37.6 $\pm$ 6.3	37.3 $\pm$ 5.6	37.7 $\pm$ 5.6	37.2 $\pm$ 5.8	36.9 $\pm$ 5.8	33.6 $\pm$ 6.3
Parity, n (%)						
Parity 1	5501 (56.6)	3641 (57.8)	1046 (52.7)	814 (56.3)	17,596 (73.7)	491,076 (43.6)
Parity $\geq$ 2	4225 (43.4)	2656 (42.2)	937 (47.3)	632 (43.7)	6409 (26.3)	636,490 (56.4)
Number of women with previous cesarean section, n (%)	1112 (11.4)	657 (10.4)	270 (13.6)	185 (12.8)	1579 (6.5)	139,624 (12.4)
Smoking, n (%)						
Yes	150 (1.5)	110 (1.7)	19 (1.0)	21 (1.5)	477 (2.0)	71,046 (6.3)
No	9128 (93.9)	5877 (93.3)	1888 (95.2)	1363 (94.3)	22,705 (93.2)	1,003,961 (89.0)
Unknown	448 (4.6)	310 (4.9)	76 (3.8)	62 (4.3)	1183 (4.9)	52,559 (4.7)
Maternal BMI, n (%)						
$<$ 18.5	150 (1.5)	86 (1.4)	35 (1.8)	29 (2.0)	393 (1.6)	25,640 (2.3)
18.5–24.9	5651 (58.1)	3638 (57.8)	1163 (58.6)	802 (55.5)	14,125 (58.0)	624,779 (55.4)
25–29.9	2305 (23.7)	1547 (24.6)	462 (23.3)	357 (24.7)	5786 (23.7)	258,742 (22.9)
$\geq$ 30	918 (9.4)	565 (9.0)	196 (9.9)	158 (10.9)	2213 (9.1)	129,896 (11.5)
Unknown	702 (7.2)	461 (7.3)	127 (6.4)	100 (6.9)	1848 (7.6)	88,509 (7.8)

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(continued)

**TABLE 1**  
**Maternal characteristics of singleton pregnancies after frozen embryo transfer (natural, stimulated, and programmed cycles), fresh embryo transfer, and spontaneous conception in Sweden, 2005–2015** (continued)

Outcome	All FET	FET, natural cycles	FET, stimulated cycles	FET, programmed cycles	Fresh embryo transfer	Spontaneous conception
<b>Maternal country of birth, n (%)</b>						
Sweden	8002 (82.3)	5169 (82.1)	1635 (82.5)	1198 (82.8)	19,853 (81.5)	858,492 (76.1)
Nordic countries outside Sweden	162 (1.7)	97 (1.5)	43 (2.2)	22 (1.5)	383 (1.6)	16,233 (1.4)
Europe outside the Nordic countries	621 (6.4)	424 (6.7)	119 (6.0)	78 (5.4)	1642 (6.7)	81,379 (7.2)
African origin	112 (1.2)	79 (1.3)	19 (1.0)	14 (1.0)	272 (1.1)	42,415 (3.8)
Asian origin	664 (6.8)	421 (6.7)	134 (6.8)	109 (7.5)	1751 (7.2)	106,677 (9.5)
Other	165 (1.7)	107 (1.7)	33 (1.7)	25 (1.7)	464 (1.9)	22,370 (2.0)
<b>Maternal education, n (%)</b>						
≤9 y	362 (3.7)	242 (3.8)	65 (3.3)	55 (3.8)	957 (3.9)	106,881 (9.5)
10–12 y	2735 (28.1)	1828 (29.0)	512 (25.8)	395 (27.3)	7203 (29.6)	411,843 (36.5)
Higher education <3 y	1330 (13.7)	875 (13.9)	246 (12.4)	209 (14.5)	3340 (13.7)	145,513 (12.9)
Higher education ≥3 y	5253 (54.0)	3321 (52.7)	1152 (58.1)	780 (53.9)	12,701 (52.1)	446,267 (39.6)
Missing	46 (0.5)	31 (0.5)	8 (0.4)	7 (0.5)	164 (0.7)	17,062 (1.5)
<b>Paternal education, n (%)</b>						
≤9 y	557 (5.7)	371 (5.9)	101 (5.1)	85 (5.9)	1591 (6.5)	128,515 (11.4)
10–12 y	3703 (38.1)	2450 (38.9)	700 (35.3)	553 (38.2)	9604 (39.4)	515,639 (45.7)
Higher education <3 y	1622 (16.7)	1022 (16.2)	346 (17.4)	254 (17.6)	3888 (16.0)	154,290 (13.7)
Higher education ≥3 y	3554 (36.5)	2234 (35.5)	795 (40.1)	525 (36.3)	8706 (35.7)	298,204 (26.4)
Missing	290 (3.0)	220 (3.5)	41 (2.1)	29 (2.0)	576 (2.4)	30,918 (2.7)
<b>Years of involuntary childlessness, n (%)</b>						
Not reported	2204 (22.7)	1337 (21.2)	507 (25.6)	360 (24.9)	4772 (19.6)	1,052,762 (93.4)
1–2 y	3535 (36.3)	2271 (36.1)	773 (39.0)	491 (34.0)	9121 (37.4)	55,963 (5.0)
3–4 y	2610 (26.8)	1758 (27.9)	470 (23.7)	382 (26.4)	7317 (30.0)	12,574 (1.1)
≥5 y	1377 (14.2)	931 (14.8)	233 (11.7)	213 (14.7)	3155 (12.9)	6267 (0.6)

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(continued)

TABLE 1

Maternal characteristics of singleton pregnancies after frozen embryo transfer (natural, stimulated, and programmed cycles), fresh embryo transfer, and spontaneous conception in Sweden, 2005–2015 (continued)

Outcome	All FET	FET, natural cycles	FET, stimulated cycles	FET, programmed cycles	Fresh embryo transfer	Spontaneous conception
Cause of infertility, <sup>a</sup> n (%)						
PCOS	1558 (16.0)	752 (11.9)	304 (15.3)	502 (34.1)	3905 (16.0)	N/A
Male factor	2613 (26.9)	1860 (29.5)	380 (19.2)	373 (25.8)	5825 (23.9)	N/A
Tubal factor	797 (8.2)	582 (9.2)	119 (6.0)	96 (6.6)	1547 (6.3)	N/A
Endometriosis	646 (6.6)	424 (6.7)	105 (5.3)	117 (8.1)	1697 (7.0)	N/A
Unexplained	3566 (36.7)	2603 (41.3)	553 (27.9)	410 (28.4)	7565 (31.0)	N/A
Other female factor	4974 (51.1)	3174 (50.4)	1015 (51.2)	785 (54.3)	12,706 (52.1)	N/A
Mixed male/female	400 (4.1)	270 (4.3)	50 (2.5)	80 (5.5)	888 (3.6)	N/A
Unknown	987 (10.1)	584 (9.3)	251 (12.7)	152 (10.5)	2743 (11.3)	N/A
Treatment type, n (%)						
IVF	5663 (58.2)	3684 (58.5)	1145 (57.7)	834 (57.7)	13,176 (54.1)	N/A
ICSI	3859 (39.7)	2613 (41.5)	838 (42.3)	612 (42.3)	10,533 (43.2)	N/A
Culture duration, n (%)						
Cleavage stage (day 2–3)	6133 (63.1)	4188 (66.5)	1069 (53.9)	876 (60.6)	20,897 (85.8)	N/A
Blastocyst stage (day 5–6)	3593 (36.9)	2109 (33.5)	914 (46.1)	570 (39.4)	3468 (14.2)	N/A
Number of embryos transferred, n (%)						
1	8475 (87.1)	5495 (87.3)	1798 (90.7)	1182 (81.7)	19,535 (80.2)	N/A
≥2	1240 (12.7)	795 (12.6)	182 (9.2)	263 (18.2)	4817 (19.8)	N/A
Missing	11 (0.1)	7 (0.1)	3 (0.2)	1 (0.1)	13 (0.1)	N/A
Number of gestational sacs, n (%)						
1	9594 (98.6)	6211 (98.6)	1957 (98.7)	1426 (98.6)	23,980 (98.4)	N/A
≥2	132 (1.4)	86 (1.4)	26 (1.3)	20 (1.4)	385 (1.6)	N/A

BMI, body mass index; FET, frozen embryo transfer; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; N/A, not available; PCOS, polycystic ovary syndrome.

<sup>a</sup> More than 1 cause possible.

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**TABLE 2**  
**Neonatal outcomes in singleton pregnancies after frozen embryo transfer (natural, stimulated, and programmed cycles), fresh embryo transfer, and spontaneous conception in Sweden, 2005–2015**

Outcome	All FET	FET, natural cycles	FET, stimulated cycles	FET, programmed cycles	Fresh embryo transfer	Spontaneous conception
Deliveries, n	9726	6297	1983	1446	24,365	1,127,566
Male sex, n (%)	4991 (51.3)	3244 (51.5)	990 (49.9)	757 (52.4)	12,406 (50.9)	580,321 (51.5)
Gestational age, mean (days) ± SD	278 ± 14.3	278 ± 14.2	278 ± 14.1	279 ± 14.9	276 ± 15.1	278 ± 12.9
Postterm ≥42 w, n (%)	584 (6.0)	363 (5.8)	93 (4.7)	128 (8.9)	1055 (4.3)	59,032 (5.2)
<37 w, n (%)	592 (6.1)	377 (6.0)	117 (5.9)	98 (6.8)	1808 (7.4)	54,417 (4.8)
<32 w, n (%)	110 (1.1)	72 (1.1)	21 (1.1)	17 (1.2)	328 (1.3)	8444 (0.7)
<28 w, n (%)	42 (0.4)	28 (0.4)	9 (0.5)	5 (0.4)	134 (0.5)	3236 (0.3)
Birthweight, mean (g) ± SD, n (%)	3590 ± 600	3580 ± 593	3581 ± 601	3650 ± 624	3419 ± 602	3538 ± 564
<2500 g, n (%)	346 (3.6)	222 (3.5)	76 (3.8)	48 (3.3)	1341 (5.5)	36,016 (3.2)
<1500 g, n (%)	77 (0.8)	51 (0.8)	16 (0.8)	10 (0.7)	285 (1.2)	7116 (0.5)
SGA <-2 SD, n (%)	271 (2.8)	179 (2.8)	54 (2.7)	39 (2.7)	1195 (4.9)	36,578 (3.2)
≥4500 g, n (%)	503 (5.2)	292 (4.6)	104 (5.2)	107 (7.4)	624 (2.6)	41,194 (3.7)
LGA >+2 SD, n (%)	637 (6.5)	386 (6.1)	139 (7.0)	112 (7.8)	862 (3.5)	50,743 (4.5)
Apgar score <7 at 5 min, n (%)	341 (3.5)	226 (3.6)	55 (2.8)	60 (4.2)	692 (2.8)	26,450 (2.3)
Perinatal mortality, n (%)	37 (0.4)	25 (0.4)	7 (0.4)	5 (0.4)	107 (0.4)	4994 (0.4)
Stillbirth, n (%)	25 (0.3)	18 (0.3)	4 (0.2)	3 (0.2)	74 (0.3)	3881 (0.3)
Neonatal mortality, n (%)	18 (0.2)	11 (0.2)	4 (0.2)	3 (0.2)	45 (0.2)	1495 (0.1)
Neonatal morbidity related to preterm birth (H35.1, P27.1, P52.5, P77), n (%)	113 (1.2)	77 (1.2)	19 (1.0)	17 (1.2)	266 (1.1)	7549 (0.7)
Sepsis, n (%)	95 (1.0)	76 (1.2)	10 (0.5)	9 (0.6)	210 (0.9)	7751 (0.7)
Meconium aspiration, n (%)	20 (0.2)	10 (0.2)	5 (0.3)	5 (0.4)	30 (0.1)	1561 (0.1)
HIE, n (%)	5 (0.1)	3 (0.0)	1 (0.0)	1 (0.1)	12 (0.0)	760 (0.1)
Major birth defects, n (%)	370 (3.8)	242 (3.8)	92 (4.6)	67 (4.6)	1079 (4.4)	38,815 (3.4)

Neonatal outcomes included neonatal morbidity related to preterm birth (retinopathy of prematurity, ICD-10 code H35.1; bronchopulmonary dysplasia, ICD-10 code P27.1; intraventricular hemorrhage grade 3, ICD-10 code P52.5; necrotizing enterocolitis, ICD-10 code P77), sepsis (ICD-10 code P36), and hypoxic ischemic encephalopathy (ICD-10 code P91.0 and P91.6).

FET, frozen embryo transfer; HIE, hypoxic ischemic encephalopathy; LGA, large for gestational age; SGA, small for gestational age.

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TABLE 3

**Maternal outcomes in singleton pregnancies after frozen embryo transfer (natural, stimulated, and programmed cycles), fresh embryo transfer, and spontaneous conception in Sweden, 2005–2015**

Outcome	All FET	FET, natural cycles	FET, stimulated cycles	FET, programmed cycles	Fresh embryo transfer	Spontaneous conception
Deliveries, n	9726	6297	1983	1446	24,365	1,127,566
Placenta previa, n (%)	107 (1.1)	73 (1.2)	21 (1.1)	13 (0.9)	509 (2.1)	3280 (0.3)
Placental abruption, n (%)	44 (0.5)	29 (0.5)	8 (0.4)	7 (0.5)	172 (0.7)	3908 (0.3)
HDP, n (%)	663 (6.8)	381 (6.1)	130 (6.6)	152 (10.5)	1268 (5.2)	44,176 (3.9)
PIH, n (%)	186 (1.9)	107 (1.7)	44 (2.2)	35 (2.4)	355 (1.5)	13,039 (1.2)
PE, n (%)	477 (4.9)	274 (4.4)	85 (4.3)	118 (8.2)	913 (3.7)	31,137 (2.8)
PPH, n (%)	943 (9.7)	497 (7.9)	165 (8.3)	281 (19.4)	1573 (6.5)	58,101 (5.2)
Cesarean section n (%)	2719 (28.0)	1665 (26.4)	573 (28.9)	481 (33.3)	6257 (25.7)	185,856 (16.5)

FET, frozen embryo transfer; HDP, hypertensive disorders in pregnancy; PE, preeclampsia; PIH, pregnancy-induced hypertension; PPH, postpartum hemorrhage.

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syndrome (AOR, 2.28; 95% CI, 1.25–4.18) compared to fresh IVF (Supplementary Table 4).

### Frozen embryo transfer vs spontaneous conception

Compared to SC, singletons born following FET have decreased risks of LBW, SGA, and stillbirth (AOR, 0.76; 95% CI, 0.67–0.86, AOR, 0.66; 95% CI, 0.58–0.75, and AOR, 0.58; 95% CI, 0.37–0.91, respectively). They were more often LGA (AOR, 1.57; 95% CI, 1.43–1.72) and macrosomic (AOR, 1.58; 95% CI, 1.43–1.76). The neonates also had an increased risk of Apgar score <7 at 5 minutes (AOR, 1.15; 95% CI, 1.01–1.30) (Supplementary Table 4).

### Maternal outcomes

#### Programmed vs natural and stimulated frozen embryo transfer

Programmed FET compared to natural FET was associated with an increased risk of HDP (AOR, 1.78; 95% CI, 1.43–2.21), PPH (AOR, 2.63; 95% CI, 2.20–3.13), and cesarean section (AOR, 1.39; 95% CI, 1.21–1.60). These differences were also seen compared to stimulated cycles (AOR, 1.61; 95% CI, 1.22–2.10, AOR, 2.87; 95% CI, 2.29–3.60, AOR, 1.27; 95% CI, 1.08–1.50, respectively) (Table 5). In a

comparison of stimulated cycles with natural cycles, a significant difference was found for cesarean section (AOR, 1.15; 95% CI, 1.01–1.30).

#### Frozen embryo transfer vs fresh in vitro fertilization

FET was associated with decreased risks of placenta previa (AOR, 0.38; 95% CI, 0.30–0.48) and placental abruption (AOR, 0.59; 95% CI, 0.41–0.85) but increased risks of HDP (AOR, 1.51; 95% CI, 1.35–1.68), PPH (AOR, 1.63; 95% CI, 1.49–1.79) and cesarean section (AOR, 1.11; 95% CI, 1.05–1.18) in comparison to fresh IVF (Supplementary Table 4).

#### Frozen embryo transfer vs spontaneous conception

FET was associated with increased risks of placenta previa (AOR, 1.76; 95% CI, 1.40–2.20), HDP (AOR, 1.20; 95% CI, 1.09–1.31), PPH (AOR, 1.74; 95% CI, 1.61–1.88), and cesarean section (AOR, 1.15; 95% CI, 1.10–1.21) compared to SC (Supplementary Table 4).

### Comment

#### Principal findings

Programmed FET was associated with increased risks of HDP, PPH, and cesarean section, in comparison to both natural and stimulated FET. These

increased risks could also be shown for FET compared to fresh IVF and SC. Singletons born following programmed FET had a greater risk of macrosomia and postterm birth compared to singletons born following natural and stimulated cycles, while no significant differences were noticed for PTB and LBW. Accordingly, an increased risk of LGA and macrosomia could be shown in FET compared to fresh IVF and SC.

#### Meaning of the findings related to other studies

Programmed FET increased the risk for HDP and PPH compared to stimulated and natural cycles. Our results are in accordance with a recent study<sup>15</sup> suggesting an increased rate of preeclampsia in programmed FET cycles where no CL is present. In a limited number of patients, that study showed highly increased rates of preeclampsia in programmed FET cycles compared to other FET protocols. The lack of circulating CL factors was suggested as a possible mechanism for these findings.<sup>17</sup> In parallel, a reduced aortic compliance has been detected in the first trimester of CL-deficient pregnancies.<sup>16</sup> Whether there is an association between excessive fetal growth and preeclampsia, especially late onset, as has been suggested in previous studies,<sup>27</sup> needs to be explored further.

TABLE 4

Neonatal outcomes (crude and adjusted odds ratios) for singleton pregnancies after stimulated vs natural cycles in frozen embryo transfer (n = 1983 stimulated cycles, n = 6297 natural cycles), programmed vs natural cycles in frozen embryo transfer (n = 1446 programmed cycles, n = 6297 natural cycles), and programmed vs stimulated cycles in frozen embryo transfer (n = 1446 programmed cycles, n = 1983 stimulated cycles)

Outcome	Stimulated vs natural cycles Crude OR (95% CI)	Stimulated vs natural cycles Adjusted <sup>a</sup> OR (95% CI)	Programmed vs natural cycles Crude OR (95% CI)	Programmed vs natural cycles Adjusted <sup>a</sup> OR (95% CI)	Programmed vs stimulated cycles Crude OR (95% CI)	Programmed vs stimulated cycles Adjusted <sup>a</sup> OR (95% CI)
Postterm $\geq 42$ w	0.80 (0.64–1.02)	0.87 (0.68–1.11)	1.59 (1.29–1.96)	1.59 (1.27–2.01)	1.97 (1.50–2.60)	1.98 (1.47–2.68)
<37 w	0.98 (0.80–1.22)	0.94 (0.74–1.19)	1.14 (0.91–1.44)	1.09 (0.85–1.40)	1.16 (0.88–1.53)	1.15 (0.84–1.57)
<32 w	0.93 (0.57–1.51)	0.78 (0.41–1.49)	1.03 (0.60–1.75)	1.23 (0.67–2.24)	1.11 (0.58–2.11)	1.54 (0.70–3.42)
<28 w	1.02 (0.48–2.17)	0.92 (0.33–2.58)	0.78 (0.30–2.02)	0.80 (0.25–2.54)	0.76 (0.25–2.28)	0.99 (0.25–4.02)
<2500 g	1.09 (0.84–1.42)	1.04 (0.77–1.40)	0.94 (0.68–1.29)	0.88 (0.62–1.26)	0.86 (0.60–1.24)	0.83 (0.55–1.27)
<1500 g	1.00 (0.57–1.75)	1.05 (0.52–2.12)	0.85 (0.43–1.68)	1.01 (0.46–2.20)	0.86 (0.39–1.89)	0.92 (0.36–2.35)
SGA <-2 SD	0.96 (0.71–1.31)	1.06 (0.76–1.47)	0.95 (0.67–1.35)	0.91 (0.62–1.35)	0.99 (0.65–1.50)	0.89 (0.56–1.43)
$\geq 4500$ g	1.14 (0.90–1.43)	1.14 (0.89–1.46)	1.64 (1.31–2.07)	1.62 (1.26–2.09)	1.44 (1.09–1.91)	1.40 (1.03–1.90)
LGA >+2 SD	1.16 (0.95–1.41)	1.11 (0.89–1.38)	1.29 (1.03–1.60)	1.27 (0.99–1.61)	1.11 (0.86–1.44)	1.10 (0.82–1.47)
Apgar score <7 at 5 minutes	0.77 (0.57–1.03)	0.75 (0.54–1.05)	1.16 (0.87–1.55)	1.09 (0.78–1.51)	1.52 (1.05–2.20)	1.46 (0.94–2.24)
Perinatal mortality	0.89 (0.38–2.06)	1.19 (0.22–6.46)	0.87 (0.33–2.28)	1.76 (0.32–9.73)	0.98 (0.31–3.09)	1.54 (0.16–14.4)
Neonatal mortality	1.16 (0.37–3.63)	0.75 (1.16–3.59)	1.19 (0.33–4.26)	1.22 (0.30–4.95)	1.03 (0.23–4.60)	1.85 (0.24–14.29)
Stillbirth <sup>b</sup>	0.71 (0.24–2.09)	1.16 (0.37–3.64)	0.73 (0.21–2.47)	1.55 (0.43–5.54)	1.03 (0.23–4.60)	1.18 (0.20–7.01)
Neonatal morbidity related to preterm birth (H35.1, P27.1, P52.5, P77)	0.78 (0.47–1.29)	0.70 (0.39–1.24)	0.96 (0.57–1.63)	0.93 (0.52–1.66)	1.23 (0.64–2.37)	1.47 (0.69–3.12)
Sepsis	0.41 (0.21–0.80)	0.45 (0.21–0.95)	0.51 (0.26–1.03)	0.51 (0.24–1.10)	1.24 (0.50–3.05)	0.94 (0.33–2.71)
Meconium aspiration	1.59 (0.54–4.66)	1.57 (0.51–4.79)	2.18 (0.74–6.39)	1.78 (0.55–5.73)	1.37 (0.40–4.75)	1.53 (0.41–5.79)
HIE	1.06 (0.11–10.18)	1.55 (0.15–16.30)	1.45 (0.15–13.97)	2.10 (0.14–31.73)	1.37 (0.09–21.95)	N/A
Major birth defects	1.01 (0.80–1.29)	1.03 (0.79–1.33)	1.01 (0.77–1.33)	0.999 (0.74–1.34)	1.00 (0.72–1.38)	0.94 (0.66–1.34)

Neonatal outcomes included neonatal morbidity related to preterm birth (retinopathy of prematurity, ICD-10 code H35.1; bronchopulmonary dysplasia, ICD-10 code P27.1; intraventricular hemorrhage grade 3, ICD-10 code P52.5; necrotizing enterocolitis, ICD-10 code P77), sepsis (ICD-10 code P36), and hypoxic ischemic encephalopathy (ICD-10 code P91.0 and P91.6).

CI, confidence interval; FET, frozen embryo transfer; HIE, hypoxic ischemic encephalopathy; LGA, large for gestational age; N/A, no adjustment made because of few events reported; OR, odds ratio; SGA, small for gestational age.

<sup>a</sup> Adjusted ORs were obtained after stratification for maternal age, body mass index, parity, year of birth of child, smoking, chronic hypertension, child's sex, level of maternal education, years of involuntary childlessness, cause of infertility, in vitro fertilization/intracytoplasmic sperm injection, freezing method (vitrification or slow-freeze), culture duration, and number of gestational sacs; <sup>b</sup> Not adjusted for level of maternal education.

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TABLE 5

**Maternal outcomes (crude and adjusted odds ratios) for singleton pregnancies after stimulated vs natural cycles in frozen embryo transfer (n = 1983 stimulated cycles, n = 6297 natural cycles), programmed vs natural cycles in frozen embryo transfer (n = 1446 programmed cycles, n = 6297 natural cycles), and programmed vs stimulated cycles in frozen embryo transfer (n = 1446 programmed cycles, n = 1983 stimulated cycles)**

Outcome	Stimulated vs natural cycles Crude OR (95% CI)	Stimulated vs natural cycles Adjusted <sup>a</sup> OR (95% CI)	Programmed vs natural cycles Crude OR (95% CI)	Programmed vs natural cycles Adjusted <sup>a</sup> OR (95% CI)	Programmed vs stimulated cycles Crude OR (95% CI)	Programmed vs stimulated cycles Adjusted <sup>a</sup> OR (95% CI)
Placenta previa	0.91 (0.56–1.49)	0.82 (0.50–1.36)	0.77 (0.43–1.40)	0.71 (0.36–1.37)	0.85 (0.42–1.70)	1.00 (0.46–2.16)
Placental abruption	0.88 (0.40–1.92)	0.75 (0.32–1.76)	1.05 (0.46–2.40)	0.93 (0.37–2.35)	1.20 (0.43–3.32)	0.56 (0.16–1.99)
HDP	1.09 (0.89–1.34)	1.05 (0.84–1.31)	1.82 (1.50–2.22)	1.78 (1.43–2.21)	1.67 (1.31–2.14)	1.61 (1.22–2.10)
PPH	1.06 (0.88–1.27)	1.05 (0.86–1.28)	2.81 (2.40–3.30)	2.63 (2.20–3.13)	2.66 (2.16–3.26)	2.87 (2.29–3.60)
Cesarean section	1.13 (1.01–1.26)	1.15 (1.01–1.30)	1.39 (1.23–1.57)	1.39 (1.21–1.60)	1.23 (1.06–1.42)	1.27 (1.08–1.50)

Maternal outcomes included placenta previa (ICD-10 code O44), placental abruption (ICD-10 code O45), hypertensive disorders in pregnancy (ICD-10 codes O13–O15), postpartum hemorrhage (ICD-10 code O72; >1000 mL).

CI, confidence interval; FET, frozen embryo transfer; HDP, hypertensive disorders in pregnancy; OR, odds ratio; PPH, postpartum hemorrhage.

<sup>a</sup> Adjusted ORs were obtained after stratification for maternal age, body mass index, parity, year of birth of child, smoking, chronic hypertension, child's sex, level of maternal education, years of involuntary childlessness, cause of infertility, in vitro fertilization/intracytoplasmic sperm injection, freezing method (vitrification or slow-freeze), culture duration, and number of gestational sacs. *Ginström Ernstad et al. Neonatal and maternal outcome depending on protocol in frozen embryo transfer. Am J Obstet Gynecol 2019.*

In our study, FET further increased the risk for HDP and PPH compared to fresh IVF and SC and decreased the risk of placental abruption in comparison with fresh embryo transfer, findings in line with several other registry studies and meta-analysis.<sup>7,11,12,28,29</sup> The finding of a higher rate of HDP in our study is also supported by a randomized controlled trial in women with PCOS in which Chen et al showed an increased risk for preeclampsia following FET.<sup>6</sup> PCOS, a more common cause of infertility in programmed and stimulated FET, is associated with an increased risk of HDP, according to a systematic review and meta-analysis.<sup>30</sup> However, in the present study we adjusted for PCOS.

In the present study, no differences were detected regarding PTB, LBW, SGA, and LGA, between different FET protocols, while a higher risk of macrosomia was seen following programmed FET. It has been suggested that the suprphysiological environment in the uterine cavity and the endometrium, caused by the hormonal stimulation in fresh IVF cycles, is a possible reason for the poorer outcome for singletons from fresh cycles compared to FET, and

elevated E<sub>2</sub> levels have been shown to be associated with LBW, SGA, and preeclampsia.<sup>31,32</sup> Although hormonal stimulation in frozen cycles is not quite comparable to stimulation during fresh cycles, the results of this study give no support for the hypothesis that the better neonatal outcome, concerning PTB, LBW, and SGA in FET cycles, is due to the lack of hormonal stimulation. Other reasons suggested to be associated with a different neonatal outcome between frozen and fresh cycles are the freezing technique per se, possible epigenetic modification following freezing/thawing, parental characteristics, and/or selection of better-quality embryos surviving both freezing and thawing. In accordance with several earlier publications, this study indicates that freezing cycles are associated with a higher risk for LGA and/or macrosomia<sup>7–10,28,33</sup> and a lower risk of LBW and being born SGA.<sup>7–9,28</sup>

### Clinical and research implications

The rate of frozen embryo transfers is steadily increasing, owing to higher success rates following blastocyst culture and new freezing techniques, such as

vitrification. Further, freeze-all strategies have gained popularity because they seem to yield similar or even higher live birth rates and decreased incidence of ovarian hyperstimulation syndrome.<sup>3–6</sup> The present study, investigating different protocols used in FET, shows increased rates of serious maternal complications, HDP, and PPH in programmed FET cycles, a reason for concern. Programmed cycles are used in anovulatory women but also in ovulatory women to avoid extensive monitoring and to be able to schedule transfers to weekdays. The proposed mechanism, absence of CL,<sup>15,16</sup> re-invents basic physiological mechanisms involved in ovulation and CL function. The results of the present study should encourage the use of natural cycles in FET, whereas programmed cycles ought to be used only when ovulation fails. The high rates of HDP and PPH noticed in programmed cycles (10.5% and 19.4%, respectively) also show similarities with oocyte donation pregnancies.<sup>34,35</sup> The reason behind the high rates of HDP and PPH in oocyte donation pregnancies is not known, but it has been suggested that they depend on immunological

mechanisms.<sup>36,37</sup> Our results may suggest another mechanism for these complications, linked to the absence of CL. Further research should, if confirming these results, investigate responsible compounds released from CL for possible use as substitution in non-ovulatory FET cycles.

### Strengths and limitations

The strength of the present study is the size of the study, consisting of a complete national birth cohort including all singletons born after FET, fresh IVF, and SC in Sweden from 2005 to 2015, minimizing the risk of selection bias. The Swedish government-administered health registries as well as national quality registries are known to have high coverage rates. The MBR is moreover known to have high validity.<sup>19–21</sup> In addition, data collection on neonatal and maternal outcomes was obtained in the same way for all groups and adjustment was made for several confounders.

A limitation of register-based studies is the risk of missing/misclassified information and the inadequate control of confounding; for example, we were not able to adjust for previous HDP or family history. Data on medications used for stimulation are not available in the Q-IVF and thus was recorded from the Prescribed Drug Register, which is a limitation of our study. We assumed that medication purchased 70 days prior to embryo transfer had been used in the analyzed cycle. Data on infertility diagnosis might be lacking, since IVF treatment is sometimes performed after minor infertility investigation and the data on diagnosis in the NPR might thus be missing. Women who conceived through ART follow the same prenatal care program as the general population, but it is of course possible that they, owing to anxiety, get more surveillance, leading to an increased detection of medical conditions. We used SC in the general population as a comparison group, whereas a more relevant comparison group would have been women with subfertility who conceived spontaneously. However, such a group is

difficult to define. We adjusted for years of infertility, well aware that the control group of SC usually is healthier and with lower risks for impaired obstetric outcomes, which might affect the results.

### Conclusion

Pregnancies after FET in natural and stimulated vs programmed cycles have a more favorable outcome, with lower rates of macrosomia, HDP, and PPH. The results support a hypothesis of a link between absence of CL in programmed cycles and adverse maternal outcomes. This is important information, since an increasing number of IVF cycles are performed as FET, including the freeze-all strategy. ■

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## Appendix

SUPPLEMENTARY TABLE 1

## Maternal and cycle characteristics of singleton pregnancies after frozen embryo transfer in stimulated and programmed cycles in Sweden, 2005–2015

Outcome	FET, stimulated cycles				FET, programmed cycles <sup>e</sup>
	Modified natural <sup>a</sup>	Ovulation induction <sup>b</sup>	FSH <sup>c</sup>	Luteal support <sup>d</sup>	
Deliveries, n	121	179	345	1338	1446
Year of birth, n (%)					
2005–2008	10 (8.3)	54 (30.2)	55 (15.9)	149 (11.1)	356 (24.6)
2009–2011	26 (21.5)	63 (35.2)	114 (33.0)	385 (28.8)	418 (28.9)
2012–2015	85 (70.2)	62 (34.6)	176 (51.0)	804 (60.1)	672 (46.5)
Maternal age, mean ± SD	35.2 ± 4.3	34.7 ± 4.6	35.9 ± 4.2	35.1 ± 4.2	34.3 ± 4.3
Maternal age (y), n (%)					
≤34	50 (41.3)	79 (44.1)	119 (34.5)	566 (42.3)	748 (51.7)
35–37	30 (24.8)	47 (26.3)	79 (22.9)	320 (23.9)	311 (21.5)
38–39	15 (12.4)	23 (12.8)	55 (15.9)	191 (14.3)	171 (11.8)
≥40	25 (20.7)	25 (14.0)	78 (22.6)	212 (15.8)	173 (12.0)
Missing	1 (0.8)	5 (2.8)	14 (4.1)	49 (3.7)	43 (3.0)
Paternal age, mean ± SD	38.1 ± 6.7	37.1 ± 5.4	38.8 ± 5.5	37.5 ± 5.5	37.2 ± 5.8
Parity, n (%)					
Parity 1	77 (63.6)	99 (55.3)	146 (42.3)	724 (54.1)	814 (56.3)
Parity ≥2	44 (36.4)	80 (44.7)	199 (57.7)	614 (45.9)	632 (43.7)
Number of women with previous cesarean section, n (%)	16 (13.2)	22 (12.3)	56 (16.2)	176 (13.2)	185 (12.8)
Smoking, n (%)					
Yes	0 (0.0)	0 (0.0)	1 (0.3)	18 (1.3)	21 (1.5)
No	117 (96.7)	165 (92.2)	330 (95.7)	1276 (95.4)	1363 (94.3)
Unknown	4 (3.3)	14 (7.8)	14 (4.1)	44 (3.3)	62 (4.3)
Maternal BMI, n (%)					
<18.5	0 (0.0)	5 (2.8)	7 (2.0)	23 (1.7)	29 (2.0)
18.5–24.9	78 (64.5)	87 (48.6)	204 (59.1)	794 (59.3)	802 (55.5)
25–29.9	27 (22.3)	41 (22.9)	79 (22.9)	315 (23.5)	357 (24.7)
≥30	9 (7.4)	26 (14.5)	32 (9.3)	129 (9.6)	158 (10.9)
Unknown	7 (5.8)	20 (11.2)	23 (6.7)	77 (5.8)	100 (6.9)
Maternal country of birth, n (%)					
Sweden	89 (73.6)	151 (84.4)	282 (81.7)	1113 (83.2)	1198 (82.8)
Nordic countries outside Sweden	6 (5.0)	1 (0.6)	7 (2.0)	29 (2.2)	22 (1.5)
Europe outside the Nordic countries	9 (7.4)	9 (5.0)	20 (5.8)	81 (6.1)	78 (5.4)
African origin	0 (0.0)	2 (1.1)	4 (1.2)	13 (1.0)	14 (1.0)
Asian origin	13 (10.7)	13 (7.3)	25 (7.2)	83 (6.2)	109 (7.5)
Other	4 (3.3)	3 (1.7)	7 (2.0)	19 (1.4)	25 (1.7)

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(continued)

SUPPLEMENTARY TABLE 1

**Maternal and cycle characteristics of singleton pregnancies after frozen embryo transfer in stimulated and programmed cycles in Sweden, 2005–2015** (continued)

Outcome	FET, stimulated cycles				FET, programmed cycles <sup>e</sup>
	Modified natural <sup>a</sup>	Ovulation induction <sup>b</sup>	FSH <sup>c</sup>	Luteal support <sup>d</sup>	
Maternal education, n (%)					
≤9 y	1 (0.8)	9 (5.0)	11 (3.2)	44 (3.3)	55 (3.8)
10–12 y	29 (24.0)	47 (26.3)	72 (20.9)	364 (27.2)	395 (27.3)
Higher education <3 y	21 (17.4)	16 (8.9)	49 (14.2)	160 (12.0)	209 (14.5)
Higher education ≥3 y	70 (57.9)	107 (59.8)	211 (61.2)	764 (57.1)	780 (53.9)
Missing	0 (0.0)	0 (0.0)	2 (0.6)	6 (0.4)	7 (0.5)
Paternal education, n (%)					
≤9 y	10 (8.3)	14 (7.8)	10 (2.9)	67 (5.0)	85 (5.9)
10–12 y	34 (28.1)	65 (36.3)	105 (30.4)	496 (37.1)	553 (38.2)
Higher education <3 y	21 (17.4)	22 (12.3)	59 (17.1)	244 (18.2)	254 (17.6)
Higher education ≥3 y	50 (41.3)	73 (40.8)	167 (48.4)	505 (37.7)	525 (36.3)
Missing	6 (5.0)	5 (2.8)	4 (1.2)	26 (1.9)	29 (2.0)
Years of involuntary childlessness, n (%)					
Not reported	21 (17.4)	44 (24.6)	84 (24.3)	358 (26.8)	360 (24.9)
1–2 y	68 (56.2)	59 (33.0)	141 (40.9)	505 (37.7)	491 (34.0)
3–4 y	23 (19.0)	56 (31.3)	71 (20.6)	320 (23.9)	382 (26.4)
≥5 y	9 (7.4)	20 (11.2)	49 (14.2)	155 (11.6)	213 (14.7)
Cause of infertility, <sup>f</sup> n (%)					
PCOS	17 (14.0)	47 (26.3)	79 (22.9)	161 (12.0)	502 (34.1)
Male factor	15 (12.4)	53 (29.6)	40 (11.6)	272 (20.3)	373 (25.8)
Tubal factor	9 (7.4)	20 (11.2)	13 (3.8)	77 (5.8)	96 (6.6)
Endometriosis	4 (3.3)	7 (3.9)	16 (4.6)	78 (5.8)	117 (8.1)
Unexplained	28 (23.1)	58 (32.4)	60 (17.4)	407 (30.4)	410 (28.4)
Other female factor	50 (41.3)	89 (49.7)	165 (47.8)	711 (53.1)	785 (54.3)
Mixed male/female	2 (1.7)	15 (8.4)	5 (1.4)	28 (2.1)	80 (5.5)
Unknown	22 (18.2)	22 (12.3)	51 (14.8)	156 (11.7)	152 (10.5)
Treatment type, n (%)					
IVF	57 (47.1)	111 (62.0)	224 (64.9)	753 (56.3)	834 (57.7)
ICSI	64 (52.9)	68 (38.0)	121 (35.1)	585 (43.7)	612 (42.3)
Culture days, n (%)					
Cleavage stage (day 2–3)	56 (46.3)	159 (88.8)	230 (66.7)	624 (46.6)	876 (60.6)
Blastocyst stage (day 5–6)	65 (53.7)	20 (11.2)	115 (33.3)	714 (53.4)	570 (39.4)
Number of embryos transferred, n (%)					
1	114 (94.2)	158 (88.3)	308 (89.3)	1218 (91.0)	1182 (81.7)
≥2	7 (5.8)	20 (11.2)	37 (10.7)	118 (8.8)	263 (18.2)
Missing	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.1)	1 (0.1)

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(continued)

## SUPPLEMENTARY TABLE 1

**Maternal and cycle characteristics of singleton pregnancies after frozen embryo transfer in stimulated and programmed cycles in Sweden, 2005–2015** (continued)

Outcome	FET, stimulated cycles				FET, programmed cycles <sup>e</sup>
	Modified natural <sup>a</sup>	Ovulation induction <sup>b</sup>	FSH <sup>c</sup>	Luteal support <sup>d</sup>	
Number of gestational sacs, n (%)					
1	121 (100.0)	174 (97.2)	342 (99.1)	1320 (98.7)	1426 (98.6)
≥2	0 (0.0)	5 (2.8)	3 (0.9)	18 (1.3)	20 (1.4)

BMI, body mass index; FET, frozen embryo transfer; FSH, follicle stimulating hormone; HT, hormone therapy; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; PCOS polycystic ovary syndrome.

<sup>a</sup> Includes human chorionic gonadotropin (hCG) as ovulation induction; <sup>b</sup> Includes clomiphene citrate or letrozole with or without hCG for ovulation induction; <sup>c</sup> The FSH group included FSH or human menopausal gonadotropin (hMG) with or without gonadotropin-releasing hormone (GnRH) agonist/antagonist; <sup>d</sup> Includes progesterone with or without hCG for ovulation induction; <sup>e</sup> Includes estrogen and progesterone with or without GnRH agonist; <sup>f</sup> More than 1 cause possible.

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SUPPLEMENTARY TABLE 2

## Neonatal outcomes in singleton pregnancies after frozen embryo transfer in stimulated and programmed cycles in Sweden, 2005–2015

Outcome	FET, stimulated cycles				FET, programmed cycles <sup>e</sup>
	Modified natural <sup>a</sup>	Ovulation induction <sup>b</sup>	FSH <sup>c</sup>	Luteal support <sup>d</sup>	
Deliveries, n	121	179	345	1338	1446
Male sex, n (%)	64 (52.9)	88 (49.2)	157 (45.5)	681 (50.9)	757 (52.4)
Gestational age, mean (days) ± SD	277 ± 15.9	277 ± 14.2	276 ± 13.6	278 ± 14.0	279 ± 14.9
Postterm ≥42 w, n (%)	4 (3.3)	8 (4.5)	9 (2.6)	72 (5.4)	128 (8.9)
<37 w, n (%)	7 (5.8)	16 (8.9)	17 (4.9)	77 (5.8)	98 (6.8)
<32 w, n (%)	2 (1.7)	1 (0.6)	4 (1.2)	14 (1.0)	17 (1.2)
<28 w, n (%)	1 (0.8)	0 (0.0)	2 (0.6)	6 (0.4)	5 (0.3)
Birthweight, mean (g) ± SD	3566 ± 666	3509 ± 656	3553 ± 563	3600 ± 596	3659 ± 624
<2500 g, n (%)	5 (4.1)	11 (6.1)	12 (3.5)	48 (3.6)	48 (3.3)
<1500 g, n (%)	2 (1.7)	2 (1.1)	2 (0.6)	10 (0.7)	10 (0.7)
SGA < -2 SD, n (%)	5 (4.1)	8 (4.5)	8 (2.3)	33 (2.5)	39 (2.7)
≥4500 g, n (%)	7 (5.8)	13 (7.3)	14 (4.1)	70 (5.2)	107 (7.4)
LGA > +2 SD, n (%)	6 (5.0)	13 (7.3)	21 (6.1)	99 (7.4)	112 (7.7)
Apgar score <7 at 5 min, n (%)	6 (5.0)	4 (2.2)	16 (4.6)	29 (2.2)	60 (4.1)
Perinatal mortality, n (%)	0 (0.0)	0 (0.0)	2 (0.6)	5 (0.4)	5 (0.3)
Stillbirth, n (%)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.2)	3 (0.2)
Neonatal mortality, n (%)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.2)	3 (0.2)
Neonatal morbidity related to preterm birth (H35.1, P27.1, P52.5, P77), n (%)	2 (1.7)	2 (1.1)	3 (0.9)	12 (0.9)	17 (1.2)
Sepsis, n (%)	0 (0.0)	3 (1.7)	2 (0.6)	5 (0.4)	9 (0.6)
Meconium aspiration, n (%)	1 (0.8)	1 (0.6)	2 (0.6)	1 (0.1)	5 (0.3)
HIE n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Major birth defects, n (%)	8 (6.6)	2 (1.1)	20 (5.8)	62 (4.6)	67 (4.6)

Neonatal outcomes included neonatal morbidity related to preterm birth (retinopathy of prematurity, ICD-10 code H35.1; bronchopulmonary dysplasia, ICD-10 code P27.1; intraventricular hemorrhage grade 3, ICD-10 code P52.5; necrotizing enterocolitis, ICD-10 code P77), sepsis (ICD-10 code P36), and hypoxic ischemic encephalopathy (ICD-10 code P91.0 and P91.6).

FET, frozen embryo transfer; FSH, follicle stimulating hormone; HIE, hypoxic ischemic encephalopathy; HT, hormone therapy; LGA, large for gestational age; SGA, small for gestational age.

<sup>a</sup> Includes human chorionic gonadotropin (hCG) as ovulation induction; <sup>b</sup> Includes clomiphene citrate or letrozole with or without hCG for ovulation induction; <sup>c</sup> The FSH group included FSH or human menopausal gonadotropin (hMG) with or without gonadotropin-releasing hormone (GnRH) agonist/antagonist; <sup>d</sup> Includes progesterone with or without hCG for ovulation induction; <sup>e</sup> Includes estrogen and progesterone with or without GnRH agonist.

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## SUPPLEMENTARY TABLE 3

## Maternal outcomes in singleton pregnancies after frozen embryo transfer in stimulated and programmed cycles in Sweden, 2005–2015

Outcome	FET, stimulated cycles				FET, programmed cycles <sup>e</sup>
	Modified natural <sup>a</sup>	Ovulation induction <sup>b</sup>	FSH <sup>c</sup>	Luteal support <sup>d</sup>	
Deliveries, n	121	179	345	1338	1446
Placenta previa, n (%)	4 (3.3)	1 (0.6)	5 (1.4)	11 (0.8)	13 (0.9)
Placental abruption, n (%)	1 (0.8)	0 (0.0)	0 (0.0)	7 (0.5)	7 (0.5)
HDP, n (%)	10 (8.3)	9 (5.0)	20 (5.8)	91 (6.8)	152 (10.5)
PIH, n (%)	5 (4.1)	4 (2.2)	9 (2.6)	26 (1.9)	35 (2.4)
PE, n (%)	5 (4.1)	5 (2.8)	11 (3.2)	65 (4.9)	117 (8.1)
PPH, n (%)	15 (12.4)	12 (6.7)	27 (7.8)	111 (8.3)	281 (19.4)
Cesarean section, n (%)	35 (28.9)	47 (26.3)	104 (30.1)	387 (28.9)	481 (33.3)

Maternal outcomes included placenta previa (ICD-10 code O44), placental abruption (ICD-10 code O45), hypertensive disorders in pregnancy (ICD-10 code O13 for pregnancy-induced hypertension and O14-O15 for preeclampsia), and postpartum hemorrhage (ICD-10 code O72; >1000 mL).

FET, frozen embryo transfer; FSH, follicle stimulating hormone; HDP, hypertensive disorders of pregnancy; HT, hormone therapy; PE, preeclampsia; PIH, pregnancy-induced hypertension; PPH, postpartum hemorrhage.

<sup>a</sup> Includes human chorionic gonadotropin (hCG) as ovulation induction; <sup>b</sup> Includes clomiphene citrate or letrozole with or without hCG for ovulation induction; <sup>c</sup> The FSH group included FSH or human menopausal gonadotropin (hMG) with or without gonadotropin-releasing hormone (GnRH) agonist/antagonist; <sup>d</sup> Includes progesterone with or without hCG for ovulation induction; <sup>e</sup> Includes estrogen and progesterone with or without GnRH agonist.

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SUPPLEMENTARY TABLE 4

**Neonatal and maternal outcomes (crude and adjusted odds ratios) for singleton pregnancies after frozen embryo transfer vs fresh embryo transfer (n = 9726 frozen and n = 24,365 fresh embryo transfers) and frozen embryo transfer vs spontaneous conception (n = 9726 frozen and n = 1,127,566 spontaneous conception)**

Outcome	FET vs fresh embryo transfer Crude OR (95% CI)	FET vs fresh embryo transfer Adjusted <sup>a</sup> OR (95% CI)	FET vs spontaneous conception Crude OR (95% CI)	FET vs spontaneous conception Adjusted <sup>a</sup> OR (95% CI)
Postterm ≥42 w	1.41 (1.27–1.57)	1.58 (1.41–1.77)	1.16 (1.06–1.26)	1.08 (0.98–1.19)
<37 w	0.81 (0.73–0.89)	0.80 (0.72–0.89)	1.28 (1.18–1.39)	0.95 (0.86–1.04)
<32 w	0.84 (0.67–1.04)	0.82 (0.63–1.07)	1.52 (1.25–1.83)	0.90 (0.71–1.15)
<28 w	0.78 (0.55–1.11)	0.82 (0.52–1.30)	1.51 (1.11–2.04)	0.89 (0.59–1.34)
<2500 g	0.63 (0.56–0.71)	0.66 (0.57–0.75)	1.12 (1.004–1.25)	0.76 (0.67–0.86)
<1500 g	0.67 (0.52–0.87)	0.70 (0.51–0.96)	1.26 (1.003–1.57)	0.76 (0.57–1.01)
SGA <-2 SD	0.56 (0.49–0.64)	0.63 (0.55–0.73)	0.85 (0.76–0.96)	0.66 (0.58–0.75)
≥4500 g	2.07 (1.84–2.34)	1.93 (1.69–2.21)	1.44 (1.31–1.57)	1.58 (1.43–1.76)
LGA >+2 SD	1.91 (1.72–2.12)	1.62 (1.44–1.82)	1.49 (1.37–1.61)	1.57 (1.43–1.72)
Apgar score <7 at 5 min	1.24 (1.09–1.42)	1.28 (1.10–1.48)	1.51 (1.36–1.69)	1.15 (1.01–1.30)
Perinatal mortality	0.87 (0.60–1.26)	0.97 (0.45–2.10)	0.86 (0.62–1.19)	0.87 (0.45–1.69)
Neonatal mortality	1.002 (0.58–1.73)	0.92 (0.48–1.75)	1.40 (0.88–2.22)	0.96 (0.55–1.68)
Stillbirth <sup>b</sup>	0.85 (0.54–1.33)	1.12 (0.65–1.92)	0.75 (0.50–1.11)	0.58 (0.37–0.91)
Neonatal morbidity related to preterm birth (H35.1, P27.1, P52.5, P77)	1.06 (0.85–1.33)	1.01 (0.78–1.31)	1.74 (1.45–2.10)	1.12 (0.90–1.40)
Sepsis	1.13 (0.89–1.45)	1.28 (0.97–1.69)	1.43 (1.16–1.75)	1.02 (0.80–1.29)
Meconium aspiration	1.67 (0.95–2.94)	2.28 (1.25–4.18)	1.49 (0.96–2.31)	1.45 (0.89–2.35)
HIE	1.04 (0.37–2.96)	1.63 (0.54–4.92)	0.76 (0.32–1.84)	0.85 (0.34–2.13)
Major birth defects	0.89 (0.80–0.998)	0.93 (0.82–1.05)	1.17 (1.07–1.29)	1.05 (0.95–1.17)
Placenta previa	0.52 (0.42–0.64)	0.38 (0.30–0.48)	3.81 (3.14–4.63)	1.76 (1.40–2.20)
Placental abruption	0.64 (0.46–0.89)	0.59 (0.41–0.85)	1.31 (0.97–1.76)	1.04 (0.75–1.46)
HDP	1.33 (1.21–1.47)	1.51 (1.35–1.68)	1.79 (1.66–1.94)	1.20 (1.09–1.31)
PPH	1.56 (1.43–1.69)	1.63 (1.49–1.79)	1.98 (1.85–2.11)	1.74 (1.61–1.88)
Cesarean section	1.12 (1.07–1.18)	1.11 (1.05–1.18)	1.97 (1.88–2.06)	1.15 (1.10–1.21)

Neonatal outcomes included neonatal morbidity related to preterm birth (retinopathy of prematurity, ICD-10 code H35.1; bronchopulmonary dysplasia, ICD-10 code P27.1; intraventricular hemorrhage grade 3, ICD-10 code P52.5; necrotizing enterocolitis, ICD-10 code P77), sepsis (ICD-10 code P36), and hypoxic ischemic encephalopathy (ICD-10 code P91.0 and P91.6).

Maternal outcomes included placenta previa (ICD-10 code O44), placental abruption (ICD-10 code O45), hypertensive disorders in pregnancy (ICD-10 codes O13–O15), postpartum hemorrhage (ICD-10 code O72; >1000 mL).

CI, confidence interval; FET, frozen embryo transfer; HDP, hypertensive disorders in pregnancy; HIE, hypoxic ischemic encephalopathy; LGA, large for gestational age; OR, odds ratio; PPH, postpartum hemorrhage; SGA, small for gestational age.

<sup>a</sup> Adjusted ORs were obtained after stratification for maternal age, body mass index, parity, year of birth of child, smoking, chronic hypertension, child's sex, level of maternal education, and years of involuntary childlessness. For comparison between assisted reproductive therapy pregnancies, stratification was also made for cause of infertility, in vitro fertilization/intracytoplasmic sperm injection, culture duration, and number of gestational sacs; <sup>b</sup> Not adjusted for level of maternal education.

Ginström Ernstad et al. Neonatal and maternal outcome depending on protocol in frozen embryo transfer. Am J Obstet Gynecol 2019.