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RESEARCH ARTICLE

Major postpartum haemorrhage after frozen embryo transfer: A population-based study

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Abstract

Objective: To investigate the effect on major postpartum haemorrhage (PPH) of mode of conception, differentiating between naturally conceived pregnancies, fresh embryo in vitro fertilisation (fresh-IVF) and frozen embryo transfer (frozen-IVF).

Design: Retrospective cohort study.

Setting: The French Burgundy Perinatal Network database, including all deliveries from 2006 to 2020, was linked to the regional blood centre database.

Population or sample: In all, 244 336 women were included, of whom 240 259 (98.3%) were singleton pregnancies.

Methods: The main analyses were conducted in singleton pregnancies, including 237 608 naturally conceived, 1773 fresh-IVF and 878 frozen-IVF pregnancies. Multivariate logistic regression models adjusted on maternal age, body mass index, smoking, parity, induction of labour, hypertensive disorders, diabetes, placenta praevia and/or accreta, history of caesarean section, mode of delivery, birthweight, birth place and year of delivery, were used.

Main outcome measures: Major PPH was defined as PPH requiring blood transfusion and/or emergency surgery and/or interventional radiology.

Results: The prevalence of major PPH was 0.74% ($n=1749$) in naturally conceived pregnancies, 1.92% ($n=34$) in fresh-IVF pregnancies, and 3.30% ($n=29$) in frozen-IVF pregnancies. The risk of major PPH was higher in frozen-IVF pregnancies than in both naturally conceived pregnancies (adjusted odds ratio [aOR] 2.63, 95% CI 1.68–4.10) and fresh-IVF pregnancies (aOR 2.78, 95% CI 1.44–5.35).

Conclusions: We found that frozen-IVF pregnancies have a higher risk of major PPH and they should be subject to increased vigilance in the delivery room.

KEY WORDS

fresh embryo in vitro fertilisation, frozen embryo transfer, major postpartum haemorrhage, matching, maternal age, multiple pregnancy, singleton pregnancy, vitrification

1 | INTRODUCTION

Transfer of frozen embryos after in vitro fertilisation (frozen-IVF) is an increasingly common procedure in Europe¹ and the USA,² accounting for almost half of the medically assisted reproduction attempts in France in 2021.³

This significant increase is firstly related to the improvement of preservation and thawing techniques. Data from the literature has shown that vitrification methods using cryoprotectant and rapid freezing have higher embryo survival and clinical pregnancy rates after thawing compared with slow freezing.⁴ There is also growing evidence that infants born

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after frozen-IVF have better perinatal outcomes compared with infants born after fresh embryo in vitro fertilisation (fresh-IVF).⁵ Another strong argument in favour of frozen-IVF treatment is the prevention of ovarian hyperstimulation syndrome, which is a major cause of maternal morbidity after IVF treatment that can lead to death.⁶

Scientific evidence appears to be increasingly in favour of frozen-IVF. However, the potential impact of frozen-IVF on severe maternal outcomes such as postpartum haemorrhage (PPH) have been much less studied.^{7–10} Postpartum haemorrhage remains one of the main direct obstetric causes of maternal mortality and is among the most frequent causes of severe maternal morbidity.^{11–13} However, previous studies on this subject present various limitations, including small sample size, no distinction on the type of pregnancy (singleton versus multiple pregnancy) or on the origin of the oocytes (autologous oocytes versus oocyte donation), relatively old data mainly focused on the slow freezing technique (and did not distinguish between slow freezing and the vitrification technique), and only partial consideration of confounding factors. The proportion of women with advanced maternal age was much higher in cases of assisted reproduction,^{8–10} which represents a potentially important source of confounding between the mode of conception and outcomes because advanced maternal age is independently associated with PPH.^{14–16} Finally, in nearly all previous studies, the definition of PPH was based on the quantified volume of blood loss (blood loss of >500, >750 or >1000 mL). This approximate visual assessment remains highly unreliable in many cases.^{17,18}

Our objective was to assess the association between mode of conception, differentiating between pregnancies conceived naturally, by fresh-IVF or by frozen-IVF and major PPH. Our analysis is focused on major PPH, clearly defined as PPH requiring blood transfusion and/or radiology and/or surgical intervention.

2 | METHODS

2.1 | Study design, data collection and anonymisation procedure

A retrospective population-level cohort study was conducted using data collected between January 2006 and December 2020 in the Burgundy Perinatal Network. The Burgundy Perinatal Network covers all public and private hospitals (four level 1 maternity wards, seven level 2 maternity wards and one level 3 maternity ward [in a university hospital]) in Burgundy, a French region with approximately 1 600 000 inhabitants.

Since 2000, all deliveries and terminations of pregnancies (around 17 000 births per year) that occur within the Burgundy Perinatal Network at or after 22 completed weeks of gestation and/or with a birthweight of 500 g or greater have been systematically recorded in the Burgundy Perinatal Network database, which is used to regularly assess maternal

and neonatal health and the medical practices within the network. Data are prospectively recorded from the mandatory discharge abstracts for each hospitalised patient (used to determine the activity-based funding of hospitals in France). In accordance with European and French law, patient data have to be rendered anonymous in each maternity unit before being sent to the Burgundy Perinatal Network unit for data validation and mother/child linkage with a success rate of 100%.¹⁹ Additional specific perinatal characteristics were also recorded prospectively from medical records and the database of the regional assisted reproductive technology (ART) centre. Data entry was overseen by the physicians in the medical records department, and our statistician compared the records compiled in our database with the birthing room registry to ensure exhaustiveness. Statistical coherence was evaluated, and any discrepancies were reported to the medical team and amended. Each year, these data are linked to the Burgundy Perinatal Network database.

Finally, data on blood transfusion from the regional blood centre (*Etablissement français du sang*) were cross-linked to the Burgundy Perinatal Network database.²⁰ The regional blood centre is the only institution authorised to collect, store and deliver blood products in France. The regional blood centre is committed to tracing any single blood unit dispensed and transfused. It has a highly reliable and exhaustive database.

These databases were rendered anonymous using ANONYMAT software¹⁹ before being sent from each hospital and from the regional blood centre, as is the usual procedure for the annual assessment of our perinatal network's performance by the regional audit committee.

2.2 | Ethics statement

The collection of data by the Burgundy Perinatal Network was approved by the French Committee for Data Protection (*Commission Nationale Informatique et Liberté*—numbers 455451 and 1363158) and this study was conducted in accordance with the Declaration of Helsinki. Written consent was not needed for this study as the database used was anonymous.

2.3 | Study population

In the current study, we restricted the analyses to women who delivered in one of the maternity wards of the Burgundy perinatal network. Terminations of pregnancy and women with fertility treatments such as intrauterine insemination were excluded.

2.4 | Outcome

The outcome was major PPH defined as PPH requiring blood transfusion (receiving at least one blood unit) and/

or emergency surgery and/or interventional radiology. Postpartum haemorrhage was identified in our database using the International Classification of Diseases 10th revision codes O72.0, O72.1 and O72.2, and was coded according to French national guidelines. The surgical and radiology technique procedures are systematically recorded in the Burgundy Perinatal Network database with the codes JNFA001 (hysterectomy), EDSA002 (hypogastric artery ligation), ELSA002 (ligation of uterine vascular pedicles for PPH by laparotomy), or EDSF011 (transcatheter uterine artery embolisation), according to the French Common Classification of Medical Procedures. Our outcome included all women with PPH from delivery up to 42 days postpartum.

2.5 | Exposure of interest

The exposure of interest in our analysis was the mode of conception, differentiated into three categories. We distinguished between women who had naturally conceived pregnancies, those with fresh-IVF, including IVF without or with intracytoplasmic sperm injection with autologous oocyte (132 pregnancies involving IVF with oocyte donation were excluded), and those with frozen-IVF.

Oocyte pick-up was performed after ovary hyperstimulation with gonadotrophin associated with pituitary gland suppression with gonadotrophin-releasing hormone agonist/antagonist. Fresh embryo transfer was associated with natural progesterone supplementation up to 7–8 weeks of gestation. Women undergoing frozen-IVF received programmed cycles, including natural estrogen and progesterone before transfer and until 12 weeks of gestation. The transfer of embryos after the vitrification freezing method was implemented in 2013. The majority of embryo transfers were performed at the early cleavage stage, in 91% of cases for fresh-IVF, and in 82% of cases for frozen-IVF.

2.6 | Covariables

The covariables were defined as follows: maternal characteristics (maternal age (<25, 25–34, ≥35 years), body mass index (BMI) before pregnancy kg/m² categorised according to World Health Organization standards (underweight <18.5 kg/m², normal 18.5–24.9 kg/m², overweight 25–29.9 kg/m², obese ≥30 kg/m²), parity (nulliparous and multiparous women), smoking during pregnancy (yes/no), history of caesarean section (yes/no), characteristics of pregnancy and labour, hypertensive disorders of pregnancy (defined as gestational hypertension, and pre-eclampsia associated or not with complications such as HELLP [haemolysis, elevated liver enzymes and low platelet count] syndrome, eclampsia and placental abruption), diabetes (gestational or other), placenta praevia and/or accreta (yes/no), induction of labour (yes/no), mode of delivery (vaginal delivery, instrumental vaginal delivery or caesarean delivery), birthweight

4000 g or greater (yes/no), birth place (level 1, 2 or 3 maternity ward) and year of birth.

2.7 | Statistical analysis

Analyses were conducted by separating singleton pregnancies (main analyses) and multiple pregnancies (secondary analyses), because the risk of serious maternal complications during pregnancy and during the postpartum period is four times higher in multiple pregnancies than in singleton pregnancies.²¹

2.7.1 | Main analysis: Singleton pregnancy

First, univariate analyses were performed to describe the population characteristics according to the mode of conception, using chi-square tests. Then, we analysed the associations between the mode of conception and major PPH with univariate and multivariate logistic regression models adjusting for potential confounding factors. These factors were maternal age, BMI, smoking during pregnancy, parity, induction of labour, hypertensive disorders of pregnancy, diabetes, placenta praevia and/or accreta, history of caesarean section, mode of delivery, birthweight of 4000 g or greater, birth place and year of delivery. Crude (OR) and adjusted (aOR) odds ratios were calculated with their 95% CI. Because there was a variation in the approach used for frozen-IVF during the study period, we performed an analysis comparing the association between the freezing method (slow-freeze versus vitrification) and major PPH.

To check the robustness of the results, two sensitivity analyses were performed.

Most covariables used in this study had an exhaustiveness of 100% or a low proportion of missing data. For this reason, analyses were first performed on complete cases. However, we also ran a sensitivity analysis using multiple imputations (chained equations with a logistic regression imputation model for missing binary data and a multinomial imputation model for missing categorical data) for variables with missing data (for example BMI was missing in 32% of cases).²² Full details are shown in Table S1. Missing data were imputed by chained equations using the SAS 'MI' procedure. Imputation model variables included maternal and neonatal characteristics: year of delivery, maternal age, smoking during pregnancy, BMI, diabetes, hypertensive disorders of pregnancy, placenta praevia and/or accreta, induction of labour, epidural analgesia, mode of delivery, birthweight, level of maternity unit, and outcomes. We generated five independent imputed data sets.

Because maternal age was the main confounder, we also performed a sensitivity analysis by matching one fresh-IVF pregnancy with three naturally conceived pregnancies, and one frozen-IVF pregnancy with three naturally conceived pregnancies on the basis of maternal age and year of delivery.

None of these variables had missing data, and this matching was used to eliminate differences in maternal age and year of delivery according to the mode of conception. The women were matched using a simple random sampling without replacement because of the large number of controls. To analyse the association between major PPH and (1) fresh-IVF versus naturally conceived pregnancies and (2) frozen-IVF versus naturally conceived pregnancies, we performed two conditional multivariate logistic regression models adjusted on BMI, smoking during pregnancy, parity, induction of labour, hypertensive disorders of pregnancy, diabetes, placenta praevia and/or accreta, history of caesarean section, mode of delivery, birthweight 4000 g or more, and birth place.

2.7.2 | Secondary analysis: Multiple pregnancy

We described the proportion of major PPH according to the mode of conception. Then, we analysed the association between the mode of conception and major PPH with univariate and multivariate logistic regression models.

Statistical significance was set at a *p* value of 0.05 for all analyses, and we applied a Bonferroni correction for multiple hypothesis testing in bivariate analyses. All analyses were performed with SAS software (version 9.2, SAS Inc., Cary, NC, USA).

3 | RESULTS

A total of 244 336 women were included, of which 240 259 (98.3%) had singleton pregnancies and 4077 (1.7%) had multiple pregnancies (Figure 1).

3.1 | Results of the main analysis

Baseline maternal and newborn characteristics are presented in Table 1. Compared with naturally conceived pregnancies, women treated for infertility were less likely to be obese or to smoke, but they had higher proportions of hypertensive disorders of pregnancy, diabetes, placenta praevia and/or accreta, had more frequent medical interventions such as induction of labour, instrumental vaginal delivery and caesarean delivery, and delivered more frequently in the level 3 maternity unit.

The prevalence of major PPH was 0.74% in naturally conceived pregnancies, 1.92% in fresh-IVF pregnancies, and 3.30% in frozen-IVF pregnancies (Table 1).

The risk of major PPH was higher in fresh-IVF pregnancies than in naturally conceived pregnancies in both the univariate (crude OR 2.64, 95% CI 1.87–3.71) and multivariate (aOR 1.66, 95% CI 1.07–2.57) analyses (Table 2).

Similarly, the risk of major PPH was higher in frozen-IVF pregnancies than in naturally conceived pregnancies in both the univariate (crude OR 4.61, 95% CI 3.17–6.69) and multivariate analyses (aOR 2.63, 95% CI 1.68–4.10) (Table 2). The

risk of major PPH was similar, whatever the freezing method (Table S2).

These results were confirmed by our sensitivity analysis. Results after multiple imputation were similar (Table S3). Our findings were also similar after matching on maternal age and year of birth plus adjusting for potential confounders (Table S4). Finally, the risk of major PPH was higher in frozen-IVF pregnancies than in fresh-IVF pregnancies (aOR 2.78, 95% CI 1.44–5.35) (Table 3). These results did not change after multiple imputation (data not shown).

3.2 | Results of the secondary analysis

The prevalence of major PPH in multiple pregnancies was 4.1% in naturally conceived pregnancies, 6.4% in fresh-IVF multiple pregnancies, and 11.1% in frozen-IVF multiple pregnancies. We observed a higher risk of major PPH both in fresh-IVF (aOR 1.60, 95% CI 1.01–2.55) and frozen-IVF (aOR 2.96, 95% CI 1.45–6.04) pregnancies than in naturally conceived pregnancies (Table 4), after adjustment for maternal age.

4 | DISCUSSION

4.1 | Principal findings

Our findings highlight that programmed frozen-IVF pregnancies had a higher risk of major PPH (i.e. requiring either blood transfusion and/or emergency surgery and/or interventional radiology) compared with naturally conceived and fresh-IVF pregnancies. We found no difference in the risk of major PPH for frozen-IVF pregnancies according to the freezing method. Furthermore, it is worrying to note that one in ten multiple pregnancies conceived by frozen-IVF may be affected by major PPH. As a result of the small number of frozen-IVF multiple pregnancies, these results should be considered as exploratory.

4.2 | Strengths and limitations of this study

The strengths of our study are that women were included from a large, prospectively collected regional cohort that provided recent, exhaustive and validated data from various types of maternity wards. In addition, to minimise the risk of selection bias, oocyte donations were excluded, and singleton and multiple pregnancies were analysed separately.

The main limitation of this study is its observational nature, so residual confounding is still possible. However, adjustment was made for several main confounders. To check the robustness of the results, we did several sensitivity analyses. For example, to mitigate the concern of missing data for some adjustment variables, we used multiple imputation to account for these missing data, which gave similar results. Numerous characteristics were collected,

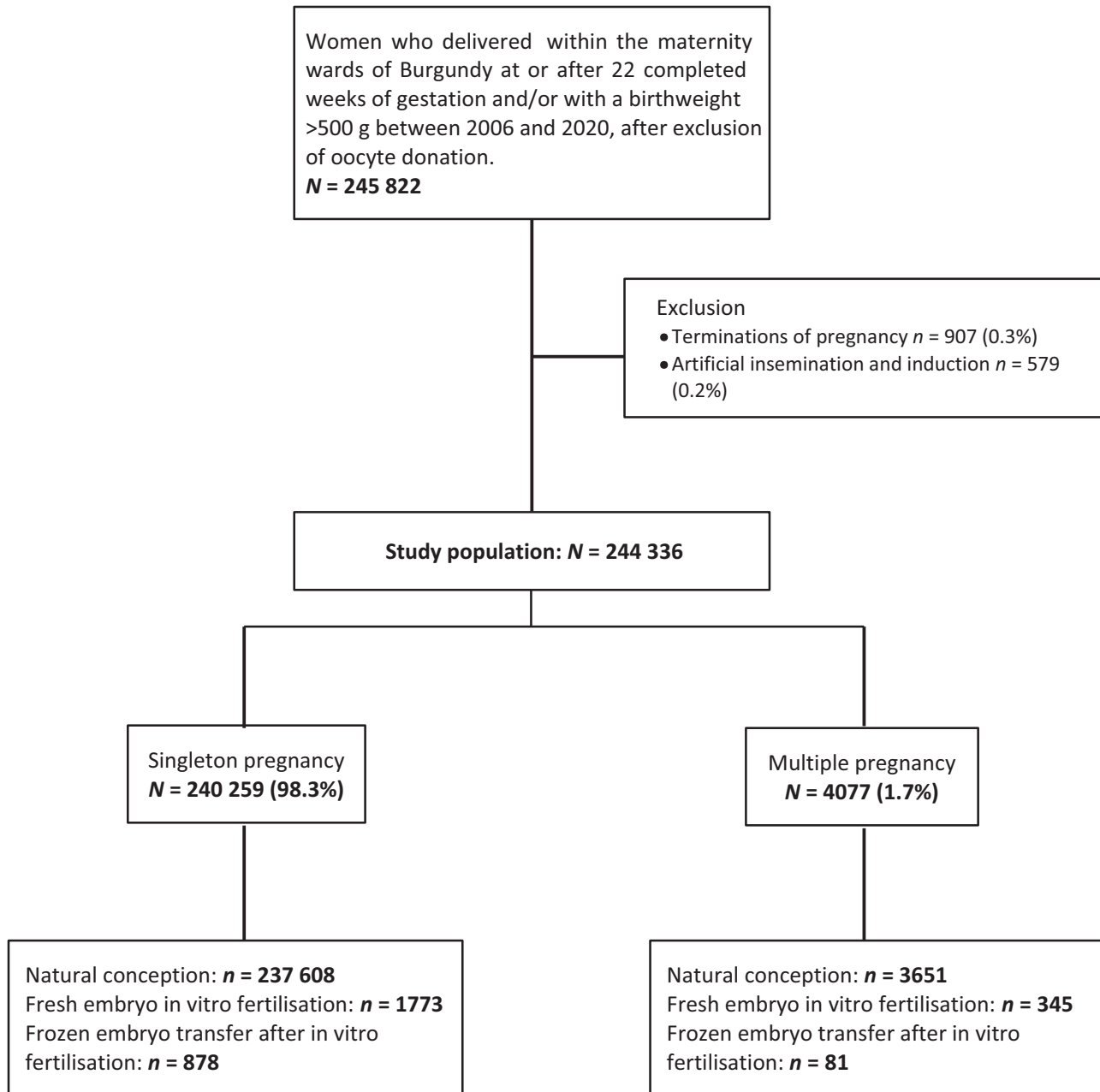


FIGURE 1 Flow chart.

but our database lacked specific information about patient history of PPH. We did not use the variable adenomyosis in our study because this information cannot be reliably obtained for the general population because the examinations required to make this diagnosis are not routinely performed in France. The quality of the collected data may vary from one maternity hospital to another. However, data collection regarding major PPH relied on the systematic collection of both blood transfusion (by the regional blood centre) and/or procedures such as emergency surgery or interventional radiology (thanks to the administrative database used for hospital budgetary allocation in the public and private sectors). Moreover, the quality and completeness of the data are evaluated locally by the

medical information departments and the statisticians of the perinatal network.

4.3 | Interpretation

Although these associations have previously been reported, the heterogeneity observed in a recent meta-analysis⁵ has raised questions about the validity of results because of some methodological aspects: the inconsistency in the definition of PPH,²³ and the lack of adjustment for confounding factors. Unlike previous studies, we focused our analyses on major PPH using a reliable indicator of maternal morbidity, as shown in previous studies.^{14,15,20,24}

TABLE 1 Perinatal characteristics in singleton pregnancy.

Characteristics ^a , n (%)	Natural conception (n = 237 608)	Fresh-IVF (n = 1773)	Frozen-IVF (n = 878)	<i>p</i> ^{b,c}
Major postpartum haemorrhage	1749/235 859 (0.74)	34/1773 (1.92)	29/878 (3.30)	<0.0001
Maternal age, years				
<25	42 436 (17.9)	55 (3.1)	14 (1.6)	<0.0001
25–35	153 539 (64.6)	1101 (62.1)	575 (65.5)	
≥35	41 633 (17.5)	617 (34.8)	289 (32.9)	
BMI, kg/m ²				
<18.5	11 614 (4.9)	85 (4.8)	48 (5.5)	<0.0001
18.5–24.9	93 159 (39.2)	902 (50.9)	471 (53.6)	
25–29.9	33 659 (14.2)	338 (19.1)	173 (19.7)	
≥30	21 625 (9.1)	199 (11.2)	84 (9.6)	
Missing	77 551	249	102	
Smoking during pregnancy	33 203 (14.0)	114 (6.5)	68 (7.7)	<0.0001
Nulliparity	86 383 (36.4)	1070 (60.4)	421 (48.0)	<0.0001
Induction of labour	28 391 (11.9)	322 (18.2)	233 (26.5)	<0.0001
Hypertensive disorders of pregnancy	9476 (4.0)	106 (5.9)	74 (8.5)	<0.0001
Diabetes	21 220 (8.9)	251 (14.2)	127 (14.5)	<0.0001
Placenta praevia and/or accreta	1398 (0.6)	43 (2.4)	17 (1.9)	<0.0001
Placenta praevia	1353 (0.6)	42 (2.4)	15 (1.7)	
Placenta accreta	69 (0.03)	1 (0.1)	2 (0.02)	
History of caesarean section	22 280 (9.4)	123 (6.9)	98 (11.2)	0.0004
Mode of delivery				
Vaginal delivery	168 284 (70.8)	1041 (58.7)	386 (44.0)	<0.0001
Instrumental delivery	29 682 (12.5)	329 (18.6)	258 (29.4)	
Caesarean delivery	39 642 (16.7)	403 (22.7)	234 (26.6)	
Birthweight, g				
<2500	14 863 (6.3)	143 (8.1)	50 (5.7)	<0.0001
2500–4000	207 760 (87.5)	1552 (87.5)	736 (83.8)	
≥4000	14 985 (6.3)	78 (4.4)	92 (10.5)	
Birth place				
Level 1 maternity unit	49 236 (20.7)	246 (13.9)	118 (13.3)	<0.0001
Level 2 maternity unit	148 191 (62.4)	752 (42.4)	343 (39.1)	
Level 3 maternity unit	40 166 (16.9)	775 (43.7)	417 (47.5)	
Missing	15			
Year of delivery				
2006–2009	69 090 (29.1)	249 (14.0)	85 (9.7)	<0.0001
2010–2013	66 327 (27.9)	413 (23.3)	164 (18.7)	
2014–2017	60 679 (25.5)	568 (32.0)	272 (31.0)	
2018–2020	41 512 (17.5)	543 (30.6)	357 (40.7)	

Abbreviations: BMI, body mass index; IVF, in vitro fertilisation.

^aDenominators vary according to the number of missing data for each variable.

^bChi-square test.

^cBonferroni correction was applied.

An increased prevalence of adenomyosis in women receiving ART may contribute to the increased PPH.⁸ However, a major role may be played by the ART procedures themselves, which have an effect on the epigenetic processes and consequently on embryonic development, and then fetal

and placental development.²⁵ Much evidence in the literature supports the hypothesis that ART induces both phenotypic and epigenetic changes in the placenta and that it could be associated with abnormal trophoblast invasion,^{26,27} and hence with adverse pregnancy outcomes.

TABLE 2 Association between the mode of conception and major postpartum haemorrhage in singleton pregnancy – univariate and multivariate analyses.

Characteristics	Major postpartum haemorrhage	
	Crude OR (95% CI)	Adjusted OR (95% CI) ^a
Mode of conception		
Natural conception	1	1
Fresh-IVF	2.63 (1.87–3.71)	1.66 (1.07–2.57)
Frozen-IVF	4.60 (3.17–6.69)	2.63 (1.68–4.10)
Maternal age, years		
<25	1.22 (1.08–1.38)	1.42 (1.21–1.66)
25–35	1	1
≥35	1.34 (1.20–1.51)	1.02 (0.87–1.19)
BMI, kg/m ²		
<18.5	0.93 (0.73–1.18)	1.17 (0.91–1.51)
18.5–24.9	0.89 (0.77–1.02)	1.05 (0.91–1.22)
25–29.9	1	1
≥30	0.80 (0.65–0.98)	0.70 (0.56–0.86)
Smoking during pregnancy		
Yes	0.90 (0.79–1.04)	0.95 (0.80–1.12)
No	1	1
Nulliparity		
Yes	1.28 (1.16–1.42)	1.07 (0.92–1.23)
No	1	1
Induction of labour		
Yes	1.59 (1.41–1.79)	1.58 (1.38–1.82)
No	1	1
Hypertensive disorders of pregnancy		
Yes	4.10 (3.59–4.68)	2.52 (2.09–3.04)
No	1	1
Diabetes		
Yes	1.19 (1.02–1.38)	0.98 (0.81–1.20)
No	1	1
Placenta praevia and/or accreta		
Yes	18.23 (15.39–21.60)	9.60 (7.47–12.35)
No	1	1
History of caesarean section		
Yes	2.23 (1.98–2.52)	1.62 (1.40–1.96)
No	1	1
Mode of delivery		
Vaginal delivery	1	1
Instrumental vaginal delivery	2.55 (2.23–2.92)	2.51 (2.12–2.97)
Caesarean delivery	4.90 (4.43–5.43)	3.51 (3.00–4.11)
Birthweight ≥4000, g		
Yes	1.88 (1.63–2.17)	2.05 (1.70–2.46)
No	1	1
Birth place		
Level 1 maternity unit	0.45 (0.38–0.52)	0.58 (0.48–0.70)
Level 2 maternity unit	0.63 (0.56–0.70)	0.86 (0.75–0.99)
Level 3 maternity unit	1	1
Year of delivery		
2006–2009	1	1
2010–2013	1.13 (0.99–1.29)	1.10 (0.91–1.32)
2014–2017	1.63 (1.44–1.85)	1.52 (1.28–1.80)
2018–2020	1.19 (1.02–1.38)	1.15 (0.94–1.40)

Abbreviations: BMI, body mass index; IVF, in vitro fertilisation.

^aMultivariate logistic regression model.**TABLE 3** Comparison of frozen-IVF and fresh-IVF for major postpartum haemorrhage in singleton pregnancy.

Outcome	Fresh-IVF ^a	Frozen-IVF
Major postpartum haemorrhage		
n/N (%)	34/1773 (1.92)	29/878 (3.30)
Crude OR (95% CI)	1	1.75 (1.06–2.90)
Adjusted OR (95% CI) ^b	1	2.78 (1.44–5.35)

Abbreviation: IVF, in vitro fertilisation.

^aReference group.^bAdjusted on: maternal age (<25, 25–34, ≥35 years old), BMI (underweight [<18.5], normal [$18.5–24.9$], overweight [$25–29.9$], obese [≥ 30]), smoking during pregnancy (yes/no), nulliparity (yes/no), induction of labour (yes/no), hypertensive disorders of pregnancy (yes/no), diabetes (yes/no), placenta praevia and/or accreta, history of caesarean section (yes/no), mode of delivery, birthweight ≥ 4000 g (yes/no), birth place, and year of delivery.**TABLE 4** Association between mode of conception and major postpartum haemorrhage in multiple pregnancy.

Outcome	Natural conception ^a	Fresh-IVF	Frozen-IVF
Major postpartum haemorrhage			
n/N (%)	151/3651 (4.1)	22/345 (6.4)	9/81 (11.1)
Crude OR ^a	1	1.57 (0.99–2.50)	2.89 (1.42–5.90)
Adjusted OR ^b	1	1.60 (1.01–2.55)	2.96 (1.45–6.04)

Abbreviation: IVF, in vitro fertilisation.

^aReference group.^bAdjusted on: maternal age.

Our results also showed an increased risk of major PPH for frozen-IVF compared with fresh-IVF. Only the freeze-thaw procedure and the duration of hormone supplementation differ between these two groups. The freeze-thaw process could contribute to the significant increase in major PPH, particularly through an impact on the trophoblast invasion process and placental vascular development. In our study, the risk of major PPH did not differ according to the method of freezing, but these results are limited because of the small numbers. The endometrial preparation could also contribute to an increased risk of PPH. In our study, it was homogeneous, because frozen embryos were transferred into the uterus after hormonal substitution (programmed frozen-IVF cycles). A recent meta-analysis showed that, compared with natural and stimulated frozen cycles, programmed frozen cycles were associated with a higher risk of PPH, but the authors point out that these results are limited by the low quality of the studies.²⁸ This is a cause for concern because for organisational reasons, most fertility centres in France primarily use programmed cycles as endometrial preparation before frozen-IVF.²⁹

To make frozen-IVF protocols safer, further studies are needed to investigate the respective role of freezing methods (i.e. embryo preparation before freezing), endometrial preparation and other environmental factors related to ART associated with major PPH.

Our findings have clinical implications. The absolute risk of major PPH for frozen-IVF in singleton pregnancy may seem low even if the percentage is much higher in frozen-IVF than in naturally conceived and fresh-IVF pregnancies. However, the number of women undergoing IVF after frozen embryo transfer is increasing worldwide,^{1,2} implying that the outcome could affect more women each year. The identification of risk factors for major PPH, which remains one of the leading causes of preventable maternal death in industrialised countries,^{30,31} is a key determinant. Birth room professionals should therefore be extra vigilant considering the risk of major PPH in these women. Currently, ART does not appear in French and international guidelines^{32,33} among the medical conditions indicating an increased risk of major PPH, suggesting that delivery should be planned in an obstetric unit equipped to manage major PPH. Our results, which are in line with previous studies,^{9,34} suggest that these recommendations could be updated. The proportion of major PPH for frozen-IVF multiple pregnancies was 11%, which means that one in ten multiple pregnancies conceived by frozen-IVF may be affected by major PPH. This proportion is almost three times higher than the rate of 4% observed in naturally conceived multiple pregnancies. These exploratory results need to be confirmed by other studies, and they raise the question of the place of birth for these pregnancies at very high risk of PPH.

5 | CONCLUSION

Our study showed that programmed frozen-IVF pregnancies have an increased risk of major PPH compared with naturally conceived and fresh-IVF pregnancies. These results are particularly important considering the increasing use of frozen embryo transfers. Given the increased risk of major PPH, frozen-IVF should be subject to increased vigilance in the delivery room.

AUTHOR CONTRIBUTIONS

This research project was conceived by Amélie Al-Khatib, Paul Sagot and Thomas Desplanches. They were involved in study design, analysis and interpretation of the results and drafted the initial manuscript and revised the manuscript. Jonathan Cottenet and Massinissa Aroun were involved in analysis and interpretation of data, and reviewed the manuscript. Catherine Quantin reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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

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