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ARTICLE

Fetal growth disorders following medically assisted reproduction: due to maternal context or techniques? A national French cohort study

BIOGRAPHY

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KEY MESSAGE

This study suggests there is an effect of medically assisted reproduction techniques on the risks for small and large for gestational age, independently of maternal context and obstetrical or neonatal morbidities. Consequences of such fetal growth disorders for long-term health of children might be noteworthy, and pathophysiological mechanisms should be further evaluated.

ABSTRACT

Research question: What part do maternal context and medically assisted reproduction (MAR) techniques play in the risk of fetal growth disorders?

Design: This retrospective nationwide cohort study uses data available in the French National Health System database and focuses on the period from 2013 to 2017. Fetal growth disorders were divided into four groups according to the origin of pregnancy: fresh embryo transfer (n = 45,201), frozen embryo transfer (FET, n = 18,845), intrauterine insemination (IUI, n = 20,179) and natural conceptions (n = 3,412,868). Fetal growth disorders were defined from the percentiles of the weight distribution according to gestational age and sex: small and large for gestational age (SGA and LGA) if <10th and >90th percentiles, respectively. Analyses were performed using univariate and multivariate logistic models.

Results: Compared with births following natural conception, multivariate analysis showed that the risk of SGA was higher for births following fresh embryo transfer and IUI (adjusted odds ratio [aOR] 1.26 [1.22–1.29] and 1.08 [1.03–1.12], respectively) and

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KEYWORDS

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significantly lower following FET (aOR 0.79 [0.75–0.83]). The risk of LGA was higher for births following FET (aOR 1.32 [1.27–1.38]), especially in artificial cycles when compared with ovulatory cycles (aOR 1.25 [1.15–1.36]). In the subgroup of births without any obstetrical or neonatal morbidity, the same increased risk of SGA and LGA were observed following fresh embryo transfer or IUI and FET (aOR 1.23 [1.19–1.27] or 1.06 [1.01–1.11] and aOR 1.36 [1.30–1.43], respectively).

Conclusions: An effect of MAR techniques on the risks for SGA and LGA is suggested independently from maternal context and obstetrical or neonatal morbidities. Pathophysiological mechanisms remain poorly understood and should be further evaluated, as well as the influence of embryonic stage and freezing techniques.

INTRODUCTION

More than 8 million children are born worldwide following treatment with assisted reproductive technologies (ART) (*Fauser, 2019*), which corresponds to 3–5% of children born each year (*Wyns et al., 2020*), and child health remains a concern for reproductive specialists. Expansion of the policy of single embryo transfer following IVF has led to a reduction in complications induced by multiple pregnancies (*Bergh et al., 2020*; *Spangmose et al., 2020*). Nevertheless, perinatal outcomes following a single pregnancy obtained by ART appear to be less favourable than in natural conception (*Pandey et al., 2012*), and could depend on the technique used. In particular, fresh embryo transfer has been associated with an increased risk of small for gestational age (SGA) and prematurity; on the other hand, frozen embryo transfer (FET) has been associated with an increased risk of large for gestational age (LGA) (*Maheshwari et al., 2018*), and could also depend on the endometrial preparation protocol (*Wang et al., 2020*). Although still poorly understood, short- and long-term consequences on children's health may prove to be serious, with some studies suggesting increased risks of cardiovascular diseases, mental health disorders and social difficulties in the case of SGA, and higher risks of obesity in childhood and adulthood in the case of LGA (*Derraik et al., 2020*; *Taal et al., 2013*).

Various causes of these poorer outcomes have been proposed, such as ovarian stimulation regimens (*Vidal et al., 2017*), embryo culture media (*Maheshwari et al., 2013*; *Wale and Gardner, 2016*), imprinting disorders (*Choux et al., 2018*) and/or subfertility itself (*Epelboin et al., 2021*; *Luke, 2017*; *Pinborg et al., 2013*). When studying the health of children born following ART, a major issue is to evaluate the respective contributions of the population characteristics and of the techniques. The choice of a relevant comparison group is challenging. Most studies use children born following natural conception as controls, making it difficult to separate the role of the ART treatment from the role of the population context, including infertility *per se*. Other approaches have been proposed, such as studying singletons born to subfertile women, either conceiving naturally with time-to-pregnancy longer than 1 year, or conceiving following intrauterine insemination (IUI) (*Pinborg et al., 2013*). Sibling studies, including couples having one child born following natural conception and one following ART, may also constitute interesting designs when adjustment is made for maternal age, parity between the two deliveries and birth order (*Henningsen et al., 2015*; *Romundstad et al., 2008*).

Despite growing literature, knowledge concerning the health of children conceived by ART remains to be explored. In particular, it has been suggested that registry studies combining ART cycle data with healthcare information could be useful, making it possible to link the parents to the child.

The present investigation aimed to evaluate the prevalence of fetal growth disorders in singleton pregnancies conceived by medically assisted reproduction (MAR) techniques as compared with natural conception. The risks of fetal growth disorders were assessed according to the MAR technique used, including IUI, IVF with fresh embryo transfer and FET, as well as according to the characteristics of the maternal population, including comorbidities and infertility causes.

MATERIALS AND METHODS

Population and data sources

The data were extracted from the French National Health System database (Système National des Données de Santé, SNDS) for the period 2013–2017. All hospitalizations in public hospitals and private clinics are registered in SNDS, which contains information on patient characteristics, diagnoses and treatments. Monitoring of pregnancies and collection of neonatal data are harmonized on the French territory and follow the evolving recommendations of the Colleges of Obstetrics and Pediatrics, including mandatory consultations, blood tests, ultrasounds and the data codification of the acts performed around the delivery. The entire follow-up is fully covered by national health insurance. All data were anonymized at data entry through specific software, making it impossible for a patient's identity to be recovered, but allowing cross-checking of information through anonymized codes. The study was piloted by a working group from the French Biomedicine Agency. Access to data was legally approved, as the French Biomedicine Agency is authorized to access the SNDS following the decree n° 2016-1871 (26 December 2016).

From this database, all singleton births (deliveries ≥22 weeks of gestation including stillbirths and medical abortion) occurring in France between 2013 and 2017 and resulting from natural conception (control group) or MAR were selected, including three groups: (i) IUI, (ii) IVF (standard or with intracytoplasmic injection) and fresh embryo transfer and (iii) FET. All deliveries with missing information or implausible data on maternal age at birth, gestational age at birth, child's sex or birthweight were excluded.

Data available in the SNDS database that concerned maternal context were the following: maternal age at the time of childbirth, primiparity, obesity (body mass index [BMI] ≥30 kg/m^2), tobacco dependence during pregnancy, history of diabetes (type 1 or 2) and hypertensive disorders, female cause of infertility, if any (endometriosis, polycystic ovary syndrome [PCOS] or premature ovarian failure [POF]), mode of conception, MAR type (if any), gestational age at birth and the child's sex and birthweight. The main identified

obstetrical morbidity indicators as per the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes in the hospitalization records were venous thrombosis, gestational diabetes, hypertensive disorders (pre-eclampsia or gestational hypertensive disorders), proteinuria, placenta praevia, placental abruption and delivery haemorrhage. The main identified neonatal morbidity indicators were congenital malformation, preterm birth (PTB, defined as neonates who were born after at least 22, but before 37 weeks of amenorrhoea), SGA (defined as neonates with a birthweight at or below the 10th percentile adjusted for gestational age and sex) and LGA (defined as neonates with a birthweight above the 90th percentile adjusted for gestational age and sex) (*Ego et al., 2016*). For FET, the endometrial preparation protocol used was identified by cross-referencing prescriptions reimbursed by national health insurance. Artificial cycles that required oestrogen prescriptions were differentiated from ovulatory cycles without any oestrogens (with either human chorionic gonadotrophin triggering or no triggering).

Statistical analysis

Characteristics of the population were described with mean and SD or with *n* (%). Quantitative variables were compared using analysis of variance (ANOVA) or chi-squared test.

The risks of SGA and LGA were evaluated according to the maternal characteristics, obstetrical morbidities and congenital malformations, and compared between four groups of conception mode, with univariate and/or multivariate analysis using a logistic regression model. Adjustments were made for maternal characteristics (age, primiparity, obesity, tobacco dependence, history of diabetes or hypertensive disorders, endometriosis, PCOS, POF), obstetrical morbidities that occurred during the pregnancy (venous thrombosis, gestational diabetes, hypertensive disorders, proteinuria, placenta praevia, placental abruption, delivery haemorrhage), mode of conception (natural conception, IUI, fresh embryo transfer, FET) and congenital malformations. Results were not adjusted for prematurity in order to avoid the risk of overadjustment, as prematurity could be a consequence of these morbidities. The prevalence of LGA in pregnancies following FET was also compared according to endometrial preparation protocols (ovulatory or artificial cycles) in univariate and multivariate analysis according to maternal characteristics, obstetrical morbidities and congenital malformations.

In order to take into account the potential impact of obstetrical morbidities on fetal growth disorders, the prevalence of SGA and LGA were also compared according to the conception mode in the subgroup of pregnancies without any obstetrical (venous thrombosis, gestational diabetes, hypertensive disorders, proteinuria, placenta praevia, placental abruption, delivery haemorrhage) or neonatal (congenital malformation, preterm birth) morbidity in multivariate analysis with adjustments for maternal characteristics.

Odds ratios (OR) and adjusted OR (aOR) with 95% confidence intervals (CI) were estimated for all variables in univariate and multivariate analysis. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc.). A *P*-value <0.05 was considered significant.

RESULTS

Between 2013 and 2017, 3,501,495 single deliveries occurred in France. Among them, 3,497,093 were included in this study due to data availability, including 84,225 following MAR, among which were 45,201 IVF and fresh embryo transfer (1.29%), 18,845 following FET (0.54%) and 20,179 following IUI (0.58%). The prevalence of SGA and LGA in the study was 10.9% (*n* = 381,093) and 11.1% (*n* = 389,690), respectively (TABLE 1). The prevalence of SGA was 14.7%, 9.4% and 12.7% in deliveries following fresh embryo transfer, FET and IUI, whereas it was 10.8% following natural conception. The prevalence of LGA was 8.8%, 13.9% and 10.1% in deliveries following fresh embryo transfer, FET and IUI, whereas it was 11.2% following natural conception.

SGA and LGA according to maternal characteristics

Maternal characteristics in singleton deliveries are presented in TABLE 2. Women who conceived by MAR were more likely to be older, nulliparous, non-smokers in contrast to women who conceived naturally. Women in MAR groups had significantly higher rates of diagnosis of PCOS or endometriosis than the natural conception group (2.4%, 2.9% and 1.8% in fresh embryo transfer, FET and IUI groups, respectively, versus 0.1%, $P < 0.0001$, for PCOS and 13.6%, 12.7% and 5.1% in fresh embryo transfer, FET and IUI groups, respectively, versus 0.8%, $P < 0.0001$, for endometriosis). A diagnosis of ovarian failure was observed in 0.04% of cases (*n* = 1403); its rate was significantly higher in fresh and FET groups (1.6% and 1.1%, respectively) in comparison to natural conception and IUI groups (0.01% and 0.2%, respectively, $P < 0.0001$).

The risk of SGA and LGA according to maternal characteristics are presented in FIGURE 1a and b, respectively. Multivariate analysis, adjusted for maternal characteristics, mode of conception, obstetrical morbidities and congenital malformations shows that the risk of SGA is higher in women under 20 or over 40 years old, while the risk of LGA increases with the age of women. Primiparity, tobacco consumption, history of hypertensive disorders or endometriosis significantly increase the risk of SGA (aOR 1.76 [1.74–1.77], 2.32 [2.29–2.35], 2.57 [2.49–2.65], 1.08 [1.05–1.11], respectively) and significantly decrease the risk of LGA

TABLE 1 PREVALENCE OF SGA AND LGA IN 3,497,093 SINGLETON DELIVERIES IN FRANCE BETWEEN 2013 AND 2017 ACCORDING TO THE MODE OF CONCEPTION

	SGA		LGA	
Conception mode	***n***	**%**	***n***	**%**
NC	370,113	10.8	381,066	11.2
Fresh ET	6656	14.7	3967	8.8
FET	1770	9.4	2610	13.9
IUI	2554	12.7	2047	10.1
Total	381,093	10.9	389,690	11.1

ET = embryo transfer; FET = frozen embryo transfer; IUI = intrauterine insemination; LGA = large for gestational age; NC = natural conception; SGA = small for gestational age.

TABLE 2 MATERNAL CHARACTERISTICS IN 3,497,093 SINGLETON DELIVERIES IN FRANCE BETWEEN 2013 AND 2017 ACCORDING TO THE MODE OF CONCEPTION

	Mode of conception								Total		*P*-value
	NC		Fresh ET		FET		IUI				
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Total	3,412,868		45,201		18,845		20,179		3,497,093		
Age (mean ± SD)	29.9 ± 5.3		33.2 ± 4.3		33.4 ± 4.3		32.6 ± 4.4				<0.0001[a]
Primiparity	1,367,579	40.1	29,356	64.9	10,399	55.2	12,811	63.5	1,420,145	40.6	<0.0001[b]
Obesity	152,825	4.5	1717	3.8	753	4.0	1025	5.1	156,320	4.5	<0.0001[b]
Tobacco dependence	145,624	4.3	952	2.1	355	1.9	419	2.1	147,350	4.2	<0.0001[b]
Hypertension	22,467	0.7	391	0.9	194	1.0	155	0.8	23,207	0.7	<0.0001[b]
Diabetes	22,727	0.7	367	0.8	142	0.8	179	0.9	23,415	0.7	<0.0001[b]
Endometriosis	27,766	0.8	6146	13.6	2393	12.7	1027	5.1	37,332	1.1	<0.0001[b]
PCOS	4970	0.1	1082	2.4	548	2.9	358	1.8	6958	0.2	<0.0001[b]
POF	430	0.0	723	1.6	200	1.1	50	0.2	1403	0.0	<0.0001[b]

Quantitative variables were compared using [a]ANOVA or [b]chi-squared test.

ET = embryo transfer; FET = frozen embryo transfer; IUI = intrauterine insemination; NC = natural conception; PCOS = polycystic ovary syndrome; POF = premature ovarian failure.

(aOR 0.59 [0.59–0.60], 0.47 [0.46–0.48], 0.82 [0.79–0.86], 0.94 [0.91–0.98], respectively), reflecting a shift in the distribution of birthweights towards lower weights. Diabetes mellitus, obesity or a diagnosis of PCOS significantly increase the risk of LGA (aOR 3.82 [3.72–3.93], 1.79 [1.76–1.81], 1.14 [1.07–1.23], respectively) and significantly decrease the risk of SGA (aOR 0.71 [0.67–0.74], 0.79 [0.78–0.81], 0.85 [0.78–0.92], respectively), representing a shift in the distribution of birthweights towards higher weights.

SGA and LGA according to the conception mode

In univariate and multivariate analysis, the risk of SGA was significantly increased in the fresh embryo transfer and IUI groups when compared with the natural conception group (aOR 1.26 [1.22–1.29] and 1.08 [1.03–1.12], respectively) and significantly decreased in the FET group compared with the natural conception group (aOR 0.79 [0.75–0.83]) (TABLE 3). Furthermore, the risk of LGA significantly increased in FET when compared with the natural conception group (aOR 1.32 [1.27–1.38]) and significantly decreased in the fresh embryo transfer group compared with the natural conception group (aOR 0.83 [0.81–0.86]). The risk of LGA was not significantly different in the natural conception and IUI groups (TABLE 3).

As far as FET are concerned, the prevalence of LGA was 12.5% or 15.1% when FET was performed during ovulatory cycles (n = 1119) or artificial cycles (n = 1491), respectively. Both in univariate and multivariate analyses, the risks of LGA significantly increased in FET groups following ovulatory or artificial cycles in comparison to the natural conception group (aOR 1.17 [1.10–1.25] and 1.46 [1.38–1.55], respectively) (TABLE 4). The risk significantly increased in artificial cycles when compared with ovulatory cycles (aOR 1.25 [1.15–1.36]).

SGA and LGA according to the conception mode in the subgroup of pregnancies with no obstetrical or neonatal morbidity

The risks of SGA and LGA according to obstetrical morbidities and congenital malformations are presented in FIGURE 2a and b, respectively. In multivariate analysis adjusted for maternal characteristics and conception mode, the risk of SGA significantly increased in case of venous thrombosis, pre-eclampsia, gestational hypertension, placenta praevia, placental abruption and congenital malformation (aOR 1.18 [1.06–1.31], 4.27 [4.19–4.35], 1.80 [1.75–1.84], 1.41 [1.32–1.51], 2.60 [2.46–2.73], 1.57 [1.54–1.59], respectively). A significantly increased risk of LGA was associated with proteinuria, gestational diabetes and delivery haemorrhage (aOR 1.35 [1.31–1.40], 1.69 [1.68–1.71], 1.68 [1.65–1.71], respectively).

In order to avoid the risk of bias in case of certain obstetrical or neonatal morbidities that could be mediators of the effect of MAR on fetal growth disorders, the risks were compared in the subgroup of pregnancies without any obstetrical or neonatal morbidity after adjustment for maternal characteristics. The risk of SGA was significantly increased in fresh embryo transfer and IUI groups when compared with the natural conception group (aOR 1.23 [1.19–1.27] and 1.06 [1.01–1.11], respectively) and significantly decreased in the FET group compared with the natural conception group (aOR 0.79 [0.75–0.84]). Furthermore, the risk of LGA was significantly higher in FET when compared with the natural conception group (aOR 1.36 [1.30–1.43]) and significantly decreased in the fresh embryo transfer group compared to the natural conception group (aOR 0.84 [0.81–0.87]) (TABLE 5).

DISCUSSION

While the health of children born following MAR represents the main issue for reproductive specialists, most study models have difficulty in properly evaluating the specific role of MAR techniques, due to potential implications related to the population context. This large national cohort study suggests an effect of MAR on the risks for fetal growth disorders, independently from maternal

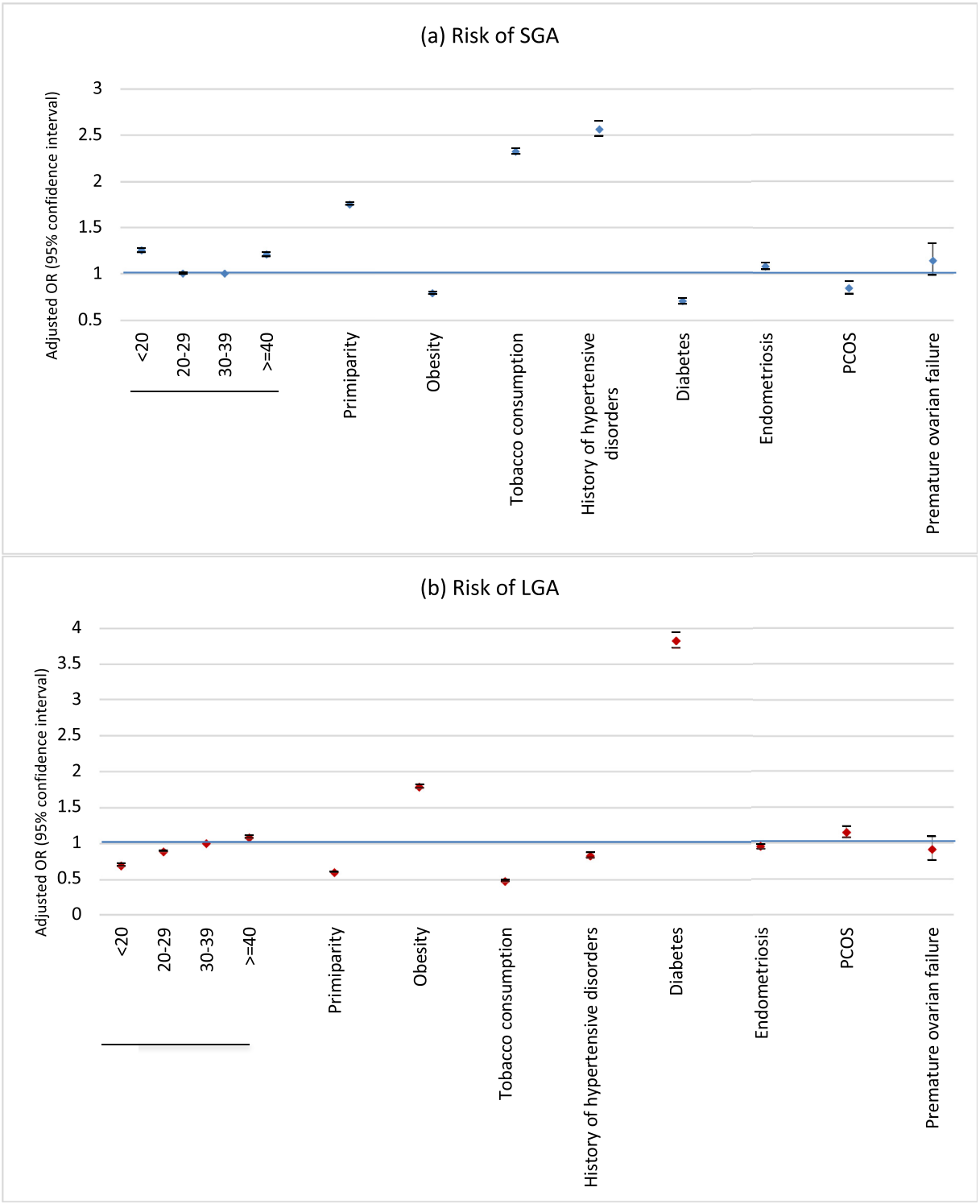

FIGURE 1 Risk of (a) SGA and (b) LGA according to maternal characteristics in multivariate analysis. The figure shows adjusted OR with 95% confidence intervals. Adjustments for maternal characteristics (barring characteristic being tested), mode of conception, obstetrical morbidities and congenital malformations. LGA = large for gestational age; OR = odds ratio; PCOS = polycystic ovary syndrome; SGA = small for gestational age.

context, or obstetrical and neonatal morbidities.

The current results show a higher risk of SGA following fresh IVF transfers when compared with natural conception, both in univariate and multivariate models adjusted for maternal population characteristics, as well as in a selected population of pregnancies without any obstetrical or neonatal morbidity. These results are in line with previously published studies suggesting a higher risk of adverse obstetrical and perinatal outcomes in singleton pregnancies following MAR

TABLE 3 RISKS OF SGA AND LGA ACCORDING TO CONCEPTION MODE BY UNIVARIATE AND MULTIVARIATE ANALYSES

SGA

Mode of conception	% (*n*/*N*)	Univariate analysis		Multivariate analysis*	
		OR [95% CI]	*P*-value	aOR [95% CI]	*P*-value
NC	10.8 (370,113/3,412,868)	Ref		Ref	
Fresh ET	14.7 (6656/45,201)	1.42 [1.38–1.46]	<0.0001	1.26 [1.22–1.29]	<0.0001
FET	9.4 (1770/18,845)	0.85 [0.81–0.89]	<0.0001	0.79 [0.75–0.83]	<0.0001
IUI	12.7 (2554/20,179)	1.19 [1.14–1.24]	<0.0001	1.08 [1.03–1.12]	0.0007
LGA					
Mode of conception	% (*n*/*N*)	Univariate analysis		Multivariate analysis[a]	
		OR [95% CI]	*P*-value	aOR [95% CI]	*P*-value
NC	11.2 (381,066/3,412,868)	Ref		Ref	
Fresh ET	8.8 (3967/45,201)	0.77 [0.74–0.79]	<0.0001	0.83 [0.81–0.86]	<0.0001
FET	13.9 (2610/18,845)	1.28 [1.23–1.33]	<0.0001	1.32 [1.27–1.38]	<0.0001
IUI	10.1 (2047/20,179)	0.90 [0.86–0.94]	<0.0001	0.96 [0.92–1.01]	0.094

aOR = adjusted odds ratio; CI = confidence interval; ET = embryo transfer; FET = frozen embryo transfer; IUI = intrauterine insemination; LGA = large for gestational age; NC = natural conception; OR = odds ratio; PCOS = polycystic ovary syndrome; POF = premature ovarian failure; Ref = reference; SGA = small for gestational age.
[a] Adjustments for maternal characteristics (age, primiparity, obesity, tobacco dependence, history of diabetes or hypertensive disorders, endometriosis, PCOS, POF), obstetrical morbidities that occurred during the pregnancy (venous thrombosis, gestational diabetes, hypertensive disorders, proteinuria, placenta praevia, placental abruption, delivery haemorrhage), and congenital malformations.

TABLE 4 RISKS OF LGA ACCORDING TO CONCEPTION MODE AND TYPE OF ENDOMETRIAL PREPARATION FOR FET BY UNIVARIATE AND MULTIVARIATE ANALYSES

LGA	**% (*n*/*N*)**				
Mode of conception		**Univariate analysis**		**Multivariate analysis[a]**	
		OR [95% CI]	***P*-value**	**aOR [95% CI]**	***P*-value**
NC	11.2 (381,066/3,412,868)	Ref		Ref	
Fresh ET	8.8 (3967/45,201)	0.77 [0.74–0.79]	<0.0001	0.83 [0.81–0.86]	<0.0001
FET – ovulatory cycle	12.5 (1119/8961)	1.14 [1.07–1.21]	<0.0001	1.17 [1.10–1.25]	<0.0001
FET – artificial cycle	15.1 (1491/9884)	1.42 [1.34–1.50]	<0.0001	1.46 [1.38–1.55]	<0.0001

aOR = adjusted odds ratio; CI = confidence interval; ET = embryo transfer; FET = frozen embryo transfer; IUI = intrauterine insemination; LGA = large for gestational age; NC = natural conception; OR = odds ratio; PCOS = polycystic ovary syndrome; POF = premature ovarian failure; Ref = reference; SGA = small for gestational age.
[a] Adjustments for maternal characteristics (age, primiparity, obesity, tobacco dependence, history of diabetes or hypertensive disorders, endometriosis, PCOS, POF), obstetrical morbidities that occurred during the pregnancy (venous thrombosis, gestational diabetes, hypertensive disorders, proteinuria, placenta praevia, placental abruption, delivery haemorrhage), and congenital malformation.

compared with naturally conceived singletons (*Pandey et al., 2012*; *Pessione et al., 2020*; *Pinborg et al., 2013*). Several physiopathological hypotheses have been raised to explain these adverse outcomes. First, the intrinsic effect of subfertility itself could affect the perinatal outcomes, and be implicated in PTB and low birthweight risks (*Pinborg et al., 2013*). Secondly, the ovarian stimulation treatment with supraphysiological serum concentrations of oestradiol and progesterone could possibly cause abnormal endometrial angiogenesis and abnormal placentation leading to growth disorders (*Pereira et al., 2015*). Third, laboratory procedures themselves, especially the embryo culture steps, may influence perinatal outcomes (*Lambert, 2003*). Although their respective responsibilities remain to be elucidated, all these factors may rely on epigenetic mechanisms that could play a key role in the correlation between children's health and conception mode (*Barberet et al., 2022*). The majority of published studies compared perinatal outcomes of singletons in subfertile couples versus fertile couples, thus making it difficult to separate the contribution of intrinsic factors of infertility from the MAR procedures. The subfertile population that conceives naturally with a time-to-pregnancy of more than 1 year or after IUI may then constitute a more appropriate group (*Pinborg et al., 2013*). Studies using this approach have demonstrated suboptimal perinatal outcomes for these couples compared with fertile couples, indicating that parental factors could contribute to the adverse events (*Epelboin et al., 2021*; *Luke, 2017*). A recent study including 117,401 singleton live births following IVF explored whether the specific cause of infertility could influence IVF perinatal outcomes. Considering

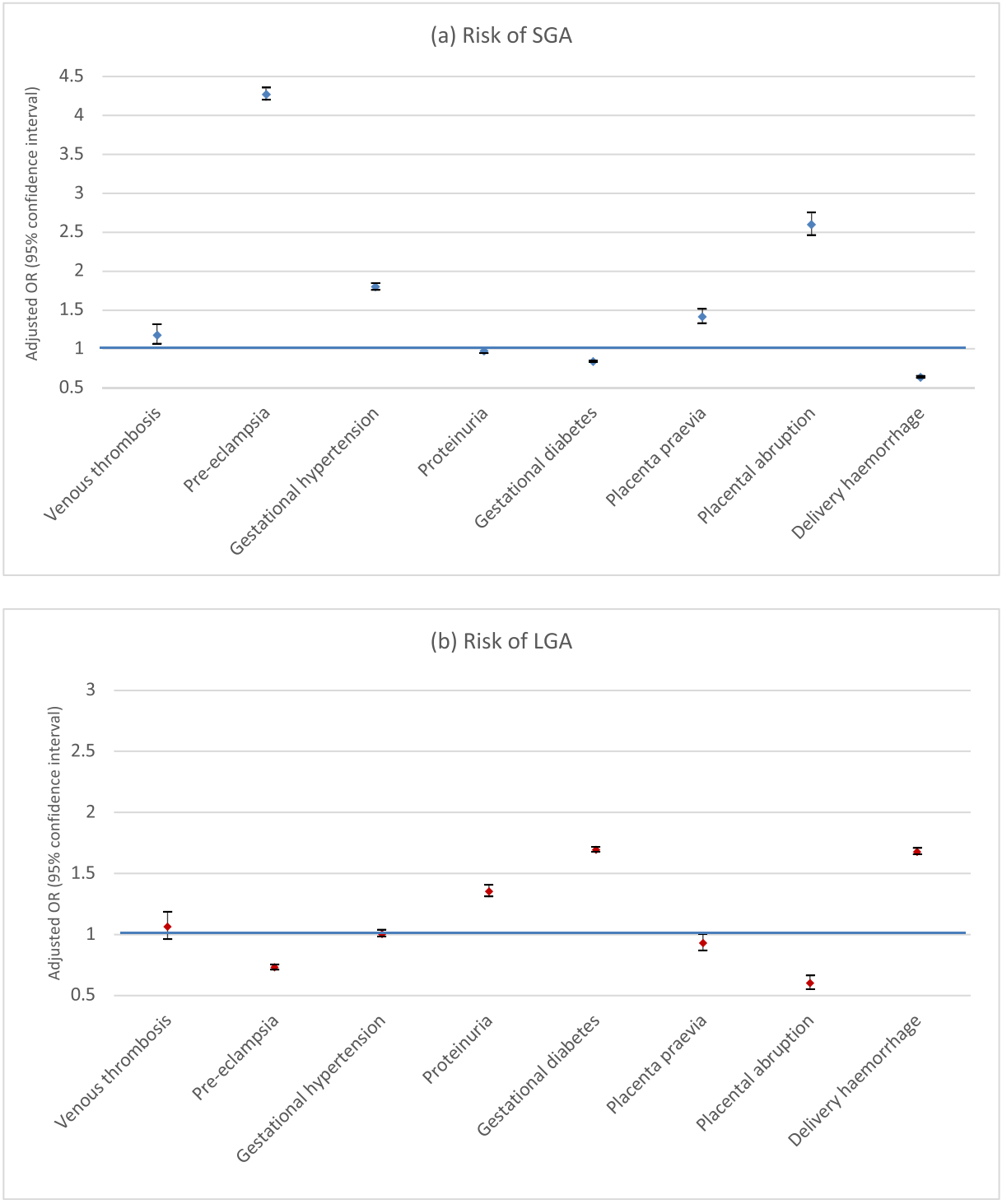

FIGURE 2 Risk of (a) SGA and (b) LGA according to obstetrical morbidities and congenital malformations in multivariate analysis. The figure shows adjusted OR with 95% confidence intervals. Adjustments for maternal characteristics (age, primiparity, obesity, tobacco dependence, history of diabetes or hypertensive disorders, endometriosis, PCOS, POF), mode of conception, obstetrical morbidities (barring morbidity being tested) and congenital malformations. LGA = large for gestational age; OR = odds ratio; PCOS = polycystic ovary syndrome; POF = premature ovarian failure; SGA = small for gestational age.

unexplained infertility as the reference group, they reported a higher risk of PTB and SGA following fresh embryo transfer in women with ovulatory or tubal disorders (*Sunkara et al., 2021*). In accordance with these findings, the current study found that pregnancies obtained after IUI were also affected by a significantly higher risk of SGA in comparison with natural conception. Although the majority of IUI are performed following ovarian stimulation, they involve monofollicular or bifollicular recruitment leading to almost physiological hormone concentrations. This result then suggests a participation of

TABLE 5 RISKS OF SGA AND LGA ACCORDING TO CONCEPTION MODE BY MULTIVARIATE ANALYSES IN A SUBGROUP OF PREGNANCIES WITHOUT ANY OBSTETRICAL OR NEONATAL MORBIDITY

SGA

Mode of conception	% (*n*/*N*)	Multivariate analysis[a]	
		aOR [95% CI]	*P*-value
NC	10.3 (289,470/2,810,831)	Ref	
Fresh ET	13.7 (4797/34,977)	1.23 [1.19–1.27]	<0.0001
FET	8.7 (1182/13,558)	0.79 [0.75–0.84]	<0.0001
IUI	12.0 (1916/15,983)	1.06 [1.01–1.11]	<0.0001

LGA

Mode of conception	% (*n*/*N*)	Multivariate analysis[a]	
		aOR [95% CI]	*P*-value
NC	10.4 (293,136/2,810,831)	Ref	
Fresh ET	8.2 (2854/34,977)	0.84 [0.81–0.87]	<0.0001
FET	13.2 (1790/13,558)	1.36 [1.30–1.43]	<0.0001
IUI	9.4 (1497/15,983)	0.97 [0.92–1.02]	0.2643

aOR = adjusted odds ratio; CI = confidence interval; ET = embryo transfer; FET = frozen embryo transfer; IUI = intrauterine insemination; LGA = large for gestational age; NC = natural conception; OR = odds ratio; PCOS = polycystic ovary syndrome; POF = premature ovarian failure; Ref = reference; SGA = small for gestational age.

[a] Adjustments for maternal characteristics (age, primiparity, obesity, tobacco dependence, history of diabetes or hypertensive disorders, endometriosis, PCOS, POF).

the infertility context in the risk of fetal growth disorder following MAR, rather than an effect of the ovarian stimulation.

Sibling studies comparing singletons born from the same mother after ART or natural conception constitute another study design to evaluate the implication of ovarian stimulation treatments and/or laboratory procedures of IVF on children's health. Even if these studies present inherent limitations, comparison of perinatal outcomes between pregnancies following IVF and natural pregnancies of the same women represents another way to separate parental and treatment contributions to perinatal health. Almost all of these studies reported a higher rate of PTB and SGA in the IVF group, indicating a specific risk attributable to the treatment with ART (*Pinborg et al., 2013*). A major recent study compared perinatal outcomes in 17,631 siblings, according to the order of the different modes of conception (natural conception, fresh embryo transfer, FET) (*Westvik-Johari et al., 2021*). After adjustments for maternal BMI and smoking, they confirmed previous results with increased odds ratios of PTB and SGA following fresh embryo transfer versus natural conception (aOR 1.27 [1.17–1.37] and 1.20 [1.09–1.34], respectively), suggesting a negative effect of ovarian stimulation on implantation and placental development (*Westvik-Johari et al., 2021*). These findings are consistent with results from studies based on an oocyte donation model. Egg donor recipients are not exposed to ovarian stimulation and have similar endometrial treatment for fresh or FET, which makes these cases very useful in evaluating differences in perinatal outcomes related to freezing/thawing embryo processes. In an oocyte donation programme comparing 360 consecutive singleton sibling pairs, *Galliano et al. (2015)* showed no difference in birthweights of newborns originating from either fresh or FET when they were delivered within the same mother. Similarly, *Vidal et al. (2017)* evaluated the perinatal outcomes in 6718 women using autologous eggs, and 7544 women using donated eggs according to the type of embryo transfer performed (fresh or FET). They reported a significantly higher risk of SGA following fresh embryo transfer when compared with FET in the autologous-egg group (8.5% and 4.8%, respectively, $P < 0.001$). In contrast, among egg donor recipients, the risk of SGA remained similar following fresh or FET (6.3% and 7.04%, respectively; $P < 0.13$) (*Vidal et al., 2017*). The current data are in line with these studies and suggest that negative perinatal outcomes are likely to be related to the detrimental effects of hyperestradiolemia on the endometrium during ovarian stimulation. Finally, *Libby et al. (2021)* analysed pregnancy outcomes in previously fertile women that had tubal ligation in comparison with infertile women. Fertile couples had similar PTB and SGA after IVF compared with infertile couples, suggesting that differences in perinatal outcomes may be due to MAR procedures rather than infertility itself (*Libby et al., 2021*).

The results of this study show a higher risk of LGA following FET when compared with natural conception, both in univariate and multivariate models adjusted for maternal characteristics, as well as in a selected population of pregnancies without any obstetrical or neonatal complications. These data confirm previously published results. Indeed, several register-based cohort studies (*Pinborg et al., 2014*; *Wennerholm et al., 2013*) and meta-analyses (*Maheshwari et al., 2018*; *Sha et al., 2018*) have shown similar and unchanged results over time with a lower risk of prematurity and hypotrophy following FET versus fresh embryo transfer, but a higher risk of fetal macrosomia (*Berntsen and Pinborg, 2018*; *Maheshwari et al., 2018*; *Sha et al., 2018*). In particular, the risk of LGA for the FET group was increased by 1.5 and 1.3 times when compared with the fresh embryo transfer and natural conception groups, respectively (*Berntsen and Pinborg, 2018*). The underlying pathophysiology of the increased risk of LGA following FET remains unclear and hypotheses involve infertility of the parents, laboratory techniques including embryo culture conditions and cryopreservation techniques, as well as endometrial preparation protocols. Cryoprotectants used for freezing could lead to epigenetic changes in early embryonic stages that may affect placental development and alter the intrauterine growth potential of the fetus (*Hiura et al., 2017*; *Pinborg et al., 2014*). Recently, *Anav et al. (2019)* analysed sibling pairs from the same embryonic cohort, the first born following fresh embryo transfer and the second following FET. The adjusted mean birthweight was significantly higher in the FET group when compared with the fresh embryo transfer group. Another recent study compared 4689 sibling groups of children conceived following FET and natural conception, in order to understand whether the higher birthweights and increased risk of LGA observed after FET only reflect the observed lower birthweight following fresh

embryo transfer when compared with natural conception (*Westvik-Johari et al., 2021*). After confounding adjustments and according to birth order, they showed that conception through FET was associated with an increased odds ratio of LGA compared with natural conception (OR 1.84 [1.56–2.17]). Studied together, these results may suggest that the cryopreservation process itself could be involved in the variation in birthweight (*Anav et al., 2019*). It is not clear whether the cryopreservation technique influences the results. Several retrospective studies have evaluated the neonatal health of children born following FET either by a slow method or vitrification when compared with fresh embryo transfer; although better neonatal outcomes were observed in both FET groups with less prematurity and hypotrophy, the same significantly increased risk of macrosomia was reported (*Belva et al., 2016*; *Li et al., 2014*), with no significant difference observed between slow freezing or vitrification (*Gu et al., 2019*; *Li et al., 2014*). Recently, in a large retrospective cohort study, *Shah et al. (2021)* evaluated perinatal outcomes in 14,424 singleton live births following fresh (n = 9280) or FET (n = 5144) in a single academic centre over 24 years. During this long period significant changes occurred, including increased use of FET, vitrification replacing slow freezing, and culture until blastocyst stage. They noted a significant decrease in the prevalence of LGA, by 1.7% annually during the entire study period. These data suggest that the evolution of clinical and IVF laboratory practices over years may partially improve IVF perinatal outcomes.

Moreover, the hormonal fluctuations induced by different endometrial preparation protocols could influence perinatal outcomes, especially because they lead to very different levels of hyperestradiolemia. Thus, this study compared the different methods of endometrial preparation for FET: ovulatory cycles using either spontaneous ovulation or mild stimulation with endogenous oestrogens, and programmed protocols involving artificial preparation with exogenous oestrogens. In a programmed cycle, oestradiol and progesterone induce endometrial proliferation and transformation, but preclude follicular maturation, ovulation and corpus luteum formation. In contrast, natural cycles or mild stimulation protocols lead to the development of a corpus luteum. In this series, it was observed that non-ovulatory cycles are associated with a higher risk of LGA when compared with ovulatory cycles, confirming previously published results (*Li et al., 2021*; *Saito et al., 2019*). There is growing evidence that absence of a corpus luteum in programmed FET cycles is associated with higher risk of hypertensive disorders in pregnancy and excess fetal growth, leading to a higher risk of LGA compared with natural or stimulated FET (*Li et al., 2021*). As oestrogen and progesterone are essential for the development of a normal placenta, inappropriate concentrations of them, as seen in programmed FET cycles, may lead to more anatomic and vascular placenta pathologies (*Albrecht et al., 2006*; *Sacha et al., 2020*). These findings could explain the increased risk of pre-eclampsia associated with programmed FET, also confirmed in the current study. A recent study suggests that the cause of the increased risk of pre-eclampsia and compromised maternal vascular health in pregnancies without corpus luteum may be due to the lack of secretion of vasoactive substances such as relaxine and vascular endothelial growth factor (*Singh et al., 2020*).

Even though the perinatal health of children born after ART has improved in recent years, evidence still shows higher risks of SGA and LGA following fresh and FET, respectively, suggesting that treatments are associated with adverse perinatal outcomes in comparison to natural conception. These adverse outcomes may have serious consequences for the short- and long-term health of children (*Derraik et al., 2020*; *Taal et al., 2013*). It is therefore essential to identify the mechanisms involved, in order to propose preventive measures or new treatment strategies to improve perinatal health in MAR-conceived children.

This study presents the first large French series evaluating fetal growth disorders in births following MAR in comparison with natural conception. The recent study period corresponds to the introduction and generalization of embryo vitrification in France, increasing the available data concerning the health of children born following embryo vitrification. All MAR techniques were evaluated, including IUI. The study thus includes a population of infertile couples who conceived without IVF, making it possible to dissociate the effect of infertility context from the effect of the techniques themselves. Not only birthweight, but weight as a function of gestational age were studied, which is now considered to be more accurate than macrosomia or hypotrophy. Data concerning maternal morbidities were available, including cause of infertility (POF, endometriosis, PCOS) and comorbidities (hypertension, diabetes, obesity, smoking). Lastly, it was possible to include the endometrial preparation protocol for FET.

The study has some limitations. Its register-based nature may limit interpretation of the results, especially as some unmeasured confounders may not have been controlled for. Given the timeframe of the study, some women may have been included more than once. Even if primiparity was considered in the statistical adjustment, slightly biased odds ratios cannot be excluded due to multiple births of higher parity for some women over the duration of the study. Data concerning the day of embryo transfer and/or freezing could not be obtained. Thus, even if some studies have suggested a higher risk of fetal growth disorder following extended embryo culture (*Marconi et al., 2022*), in this series, pregnancies would have been obtained following either conventional IVF or ICSI, and cleaved embryo transfers or blastocyst transfers. Moreover, perinatal growth of children born after FET between 2013 and 2017 were evaluated, regardless of the freezing date and technique, and no data concerning freeze devices or media were available. The protocols used for endometrial preparation for FET were extracted according to drug prescriptions, which could lead to some imprecision. Finally, no data were available concerning potential treatments for prophylaxis of fetal growth disorders, such as aspirin.

In conclusion, the current results show a higher risk of SGA and LGA following fresh and FET, respectively. The origin of these fetal growth disorders is probably multifactorial, combining maternal context, obstetric and neonatal pathologies, but also infertility context *per se*, as suggested by the higher risk of SGA observed for pregnancies obtained following IUI. However, even if respective roles remain difficult to identify and laboratory procedures may influence the outcomes, ovarian stimulation impact seems to prevail for SGA risk following IVF and endometrial preparation protocols for LGA after FET. In this context, the benefit of a freeze-all strategy followed by FET in an ovulatory cycle, as well as the interest in some medical treatments for reducing the risk for fetal growth disorder should be

further evaluated, especially in women presenting risk factors. Finally, further long-term studies should be planned in order to evaluate the consequences for future health of the identified fetal growth disorders.

AUTHOR ROLES

NS: analysis and interpretation of data; writing of the manuscript. LH: analysis and interpretation of data; writing of the manuscript. JDM: interpretation of data, critical revisions of the manuscript. AV: interpretation of data, critical revisions of the manuscript. SE: interpretation of data, critical revisions of the manuscript. PF: interpretation of data, critical revisions of the manuscript. MJGB: interpretation of data, critical revisions of the manuscript. JL: interpretation of data, critical revisions of the manuscript. GV: interpretation of data, critical revisions of the manuscript. MB: study design, collection of data, critical revisions of the manuscript. CD: study design, collection of data, critical revisions of the manuscript. PJ: study design, collection of data, critical revisions of the manuscript. RL: study design, interpretation of data, critical revisions of the manuscript. FP: study design; collection of data; statistical analysis; interpretation of data; critical revisions of the manuscript.

DATA AVAILABILITY

Data will be made available on request.

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