

Peripartum and postpartum outcomes in uncomplicated term pregnancy following ART: a retrospective cohort study from two Italian obstetric units

Silvia Vannuccini^{1,2}, Chiara Ferrata², Federica Perelli²,
Serena Pinzauti², Filiberto M. Severi¹, Fernando M. Reis^{1,3},
Felice Petraglia^{4,*} , and Mariarosaria Di Tommaso²

¹Obstetrics and Gynecology, Department of Molecular and Developmental Medicine, University of Siena, 'S. Maria alle Scotte' University Hospital, viale Bracci, 53100 Siena, Italy ²Department of Health Sciences, University of Florence, Careggi University Hospital, Largo Brambilla, 50134 Florence, Italy ³Department of Obstetrics and Gynecology, Universidade Federal de Minas Gerais, 30130-100 Belo Horizonte, Brazil ⁴Department of Biomedical, Experimental and Clinical Sciences 'Mario Serio', University of Florence, Careggi University Hospital, Largo Brambilla, 50134 Florence, Italy

*Correspondence address. Department of Biomedical, Experimental and Clinical Sciences 'Mario Serio', University of Florence, Careggi University Hospital, Largo Brambilla, 50134 Florence, Italy. E-mail: felice.petraglia@unifi.it  orcid.org/0000-0002-8851-625X

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STUDY QUESTION: Do singleton uncomplicated term pregnancies conceived by assisted reproductive technology (ART) have adverse peripartum and postpartum outcomes?

SUMMARY ANSWER: Term pregnancies following ART, even if uncomplicated until birth, have a higher risk of retained placenta and postpartum hemorrhage (PPH).

WHAT IS KNOWN ALREADY: There is consistent evidence that pregnancies following ART have higher incidence of complications during pregnancy. However, few studies specifically investigated birth outcomes in ART term pregnancies.

STUDY DESIGN, SIZE, DURATION: A retrospective cohort study was conducted on 14 415 deliveries at two university tertiary care obstetric units. Clinical data were extracted by reviewing obstetric records of all deliveries from 1 January 2010 to 31 December 2014, in a standardized electronic database regarding the mother's health before and during pregnancy, complications during pregnancy and at birth, and neonatal outcome.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Following an accurate evaluation of exclusion criteria (multiparity, maternal pre-pregnancy diseases, prior uterine surgery, fetal malformations, intrauterine deaths, elective cesarean section and pregnancy complications), the group of uncomplicated singleton term pregnancies from autologous ART conception by *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) ($n = 188$) was compared with a maternal age and body mass index (BMI) matched group of spontaneous pregnancies ($n = 1168$). Cases of intrauterine insemination (IUI) ($n = 14$) and ovulation induction with timed intercourse ($n = 18$) were not included. Labor, delivery and postpartum outcomes were evaluated. Odds ratios (OR) were adjusted with multivariable logistic regression to maternal age, BMI, nationality and gestational age at birth.

MAIN RESULTS AND THE ROLE OF CHANCE: The age of women in the final analysis ranged from 25 to 45 years, while BMI ranged from 17 to 34 kg/m². Uncomplicated term pregnancies with ART conception had a higher risk of operative delivery (adjusted OR 1.40, 95% confidence interval (CI) 1.01–1.95), retained placenta (adjusted OR 2.63, 95% CI 1.31–5.26) and PPH (adjusted OR 2.86 95% CI 1.37–5.99). Conversely, ART conception did not increase the risk of induced labor (adjusted OR 1.18, 95% CI 0.85–1.65). However, patients that conceived by ART and underwent labor induction had a higher risk of failed induction compared with the control group (adjusted OR 2.53, 95% CI 1.23–5.21). Infants born after ART had a similar birthweight, Apgar score and arterial blood pH compared with spontaneously-conceived ones.

LIMITATIONS, REASONS FOR CAUTION: The database lacked specific information about causes of infertility, smoking habit, family income and details on ART (fresh versus frozen cycle, IVF versus ICSI), limiting, in part, our analysis of the results. However, only autologous IVF/ICSI pregnancies were included in order to prevent bias related to conception by oocyte/embryo donation. *In vivo* conception ART cases were excluded because they were too few to allow comparison with IVF/ICSI. Nevertheless, the inclusion of only uncomplicated pregnancies provides a highly homogeneous and still representative population sample. Study sample is representative of a well-resourced obstetric facility in a high-income country, limiting to some extent the generalizability of study results.

WIDER IMPLICATIONS OF THE FINDINGS: Pregnancies conceived by autologous ART that proceed uncomplicated until term may require counseling about the risk of placental retention with PPH.

STUDY FUNDING/COMPETING INTERESTS: The authors have no conflict of interest and funding to declare.

Key words: ART / delivery / induction of labor / infertility / IVF / operative delivery / neonatal outcome / postpartum hemorrhage / retained placenta / uncomplicated pregnancy

WHAT DOES THIS MEAN FOR PATIENTS?

This study looked at births after fertility treatment to see whether there were any additional complications with IVF. There has been evidence in the past to suggest that there may be more complications in pregnancy after IVF, but it is not always clear whether this may in part be linked to factors other than the treatment.

The researchers looked at more than 8000 births at two hospitals in Italy, ruling out any births where there had been problems during the pregnancies or where the mothers had pre-existing medical conditions. They matched characteristics such as the age and BMI of the mothers to ensure they were comparing like with like. All the pregnancies had progressed without any complications until the mother went into labor.

They found that even when the IVF pregnancies had been problem-free, there was a higher chance of the placenta being retained and of hemorrhage after birth, and a greater risk of induction not working and of having a forceps or ventouse for the birth. The study did not specify whether the women had IVF or ICSI or whether they had a frozen or fresh treatment cycle. The researchers say further studies are needed to investigate the reasons behind these differences.

Introduction

In the last few decades, the number of women having *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) has increased worldwide (Ishihara et al., 2015; Williams et al., 2015) and there is consistent evidence that pregnancies following assisted reproductive technology (ART) have a higher risk of adverse obstetric and perinatal outcomes (Helmerhorst et al., 2004; Romundstad et al., 2006, 2008). This is attributed to the higher proportion of multiple pregnancies, but data available from systematic reviews showed that singleton pregnancies conceived after ART are at increased risk of preterm birth, hypertensive disorders, antepartum and postpartum hemorrhage (PPH), placental disorders and low birthweight infants (Pandey et al., 2012; Pinborg et al., 2013; Malchau et al., 2014; Qin et al., 2015). These factors were also associated with an increased incidence of cesarean deliveries (Helmerhorst et al., 2004) and induction of labor in women with singleton pregnancies (Pandian et al., 2001).

Although many studies have attempted to evaluate obstetric and perinatal outcomes in women conceiving with the aid of ART, it is unclear whether ART procedures or maternal factors associated with infertility, such as maternal age, BMI, past obstetric outcome and medical history, contribute to these adverse outcomes (Hayashi et al., 2012; Raatikainen et al., 2012; Farhi et al., 2013; Messerlian et al., 2013; Stern et al., 2015). Despite the specific limitations of each study, the association of ART with poor obstetric and perinatal outcome is relevant (Barnhart, 2013; Vannuccini et al., 2016).

Unfortunately, few studies specifically investigated birth outcomes in full-term ART pregnancies. Indeed, previous reports included both complicated and uncomplicated pregnancies, so labor and delivery were managed according to the potential presence of an obstetric complication or pre-pregnancy diseases (Hayashi et al., 2012; Sun et al., 2014). In addition, a significant number of women underwent elective cesarean section (CS) on maternal request, even if the pregnancies were uncomplicated until term (Gillet et al., 2011).

Thus, the aim of this study was to evaluate the perinatal outcomes of singleton uncomplicated term pregnancies from ART conception in comparison with maternal age and BMI-matched term pregnancies from spontaneous conception.

Materials and Methods

A retrospective cohort study was conducted on 14415 deliveries at the Careggi University Hospital in Florence and at the University Hospital in Siena, Italy. Clinical data were extracted by reviewing obstetric records of all deliveries from 1 January 2010 to 31 December 2014, in a standardized electronic database regarding the mother's health before and during pregnancy, complications during pregnancy and at birth, and neonatal outcome. The research protocol involved only existing records, based on information routinely collected and stored in a de-identified dataset and hence was considered exempt from ethical review board approval and a requirement for written informed consent.

Maternal characteristics included age, pre-pregnancy BMI, parity, pre-existing maternal diseases and history of treatment for infertility, such as

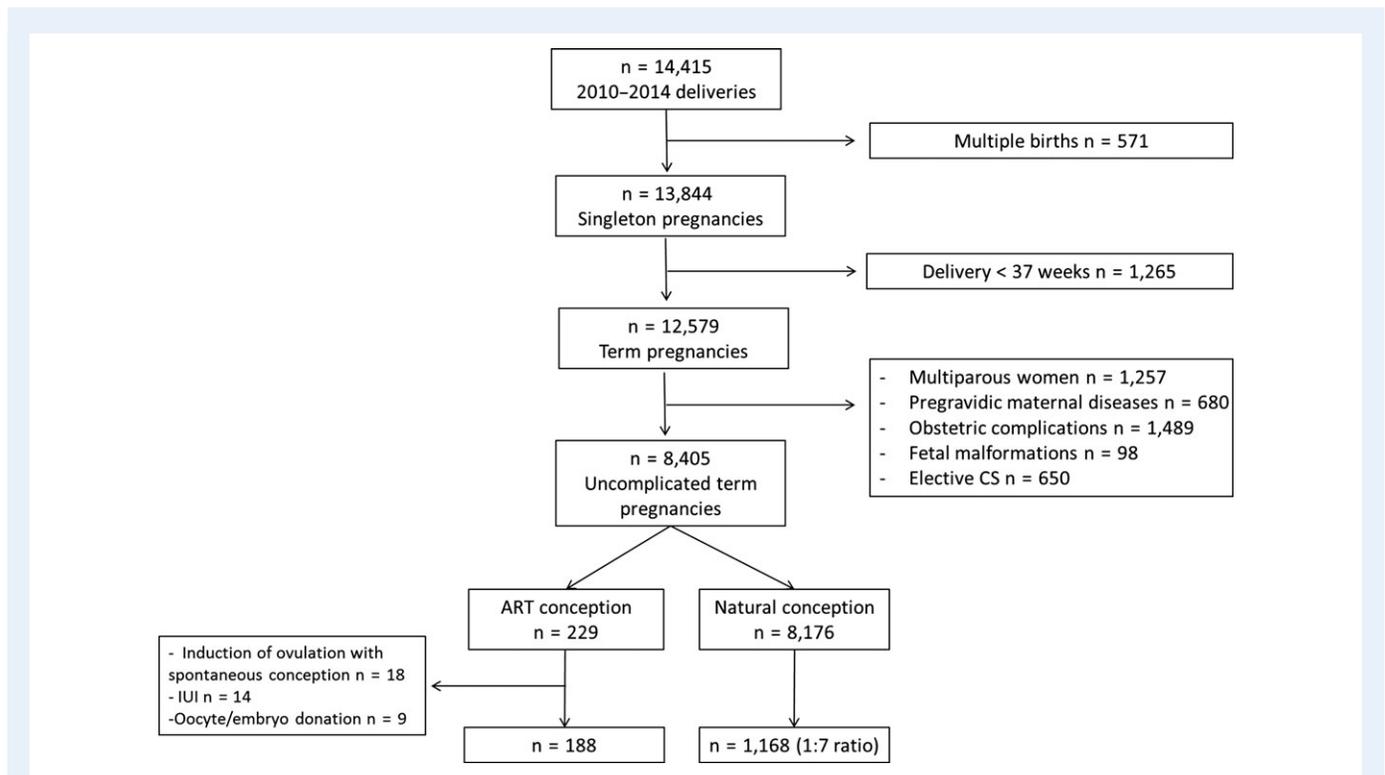


Figure 1 Flow chart of the population in a study of peripartum and postpartum outcomes in uncomplicated term pregnancy following ART.

ovulation stimulation, IUI or IVF with or without ICSI and embryo transfer. Complications that occurred during pregnancy and all data regarding birth, including neonatal outcome, were extracted. These data conform to uniform coding specifications, have passed a rigorous quality check, and have been edited and reviewed by two different data managers for each institution.

The flow diagram for study population selection is shown in Fig. 1. From the initial dataset of all deliveries ($n = 14\,415$), the group was limited to singleton term pregnancies between 37 and 42 weeks gestational age ($n = 12\,579$). To limit confounding, the following exclusion criteria were applied: multiparity, maternal pre-pregnancy diseases (diabetes, chronic hypertension, thyroid disease, renal disease, neurological diseases, inflammatory rheumatic diseases, respiratory diseases and gynecologic diseases, such as uterine fibroids, polycystic ovary syndrome (PCOS) and endometriosis), prior uterine surgery, obstetric complications diagnosed during pregnancy until labor onset (hypertensive disorders, gestational diabetes, obstetric cholestasis, intrauterine growth restriction, small-for-gestational age babies, oligo-polyhydramnios, placental diseases, placental abruption), fetal malformations, intrauterine deaths and elective CS (for breech or transverse fetal lie), including CS on maternal request.

The final cohort included 8405 uncomplicated term pregnancies, either following ART ($n = 229$) or spontaneous ($n = 8\,176$) conception. Singleton term pregnancies with autologous IVF/ICSI conception (excluding oocyte/embryo donation) were included in the study as the exposed group ($n = 188$). Cases of IUI ($n = 14$) and ovulation induction with timed intercourse ($n = 18$) were not included because they were too few to allow comparison with IVF/ICSI. Singleton pregnancies with spontaneous conception (non-exposed group) were matched to the exposed group for age and BMI (1:7 ratio) ($n = 1\,168$). The age ranged from 25 to 45 years, while BMI ranged from 17 to 34 kg/m².

The following outcome measures related to birth and postpartum were evaluated: induction of labor, failed induction, length of active phase of labor, mode of delivery (spontaneous vaginal delivery, operative vaginal delivery or CS), 'in labor' CS, retained placenta, PPH, episiotomy and

third/fourth degree perineal tears, neonatal birthweight, Apgar scores and umbilical cord blood gas analysis. The main indications for labor induction were prolonged rupture of membranes and late-term (41 completed weeks) pregnancy. Indications for 'in labor' CS were: non-reassuring fetal heart tracing, fetal distress, failure to progress (arrest of dilation or descent) or cephalopelvic disproportion.

Statistical analysis

Data were analyzed using GraphPad Prism version 5.00 for Windows (GraphPad Software, Inc, San Diego, CA, USA) and IBM SPSS version 22 (IBM, Armonk, NY, USA) statistical software packages. Data distribution was evaluated by the D'Agostino & Pearson omnibus normality test. Two-group comparisons were performed using Chi-square test with continuity correction or Fisher's exact test for binomial variables, while Mann-Whitney *U* test was used for quantitative variables, which were expressed both as mean \pm SD and median with interquartile range. *P*-values of <0.05 were considered to indicate statistical significance. Odds ratios (OR) and 95% confidence interval (CI) were calculated for each outcome and adjusted for maternal age, BMI, nationality and gestational age at birth using multivariable backward stepwise (conditional) logistic regression.

The study sample was calculated to detect a minimal effect size of two-fold increase (from an estimated 5% to 10%) in the risk of retained placenta, PPH, acute fetal distress or fetal hypoxemia, with a statistical power of 80% and confidence level of 95% (Chow et al., 2008).

Results

Maternal and perinatal characteristics of the study population are shown in Table 1. The group of women with ART conception had similar gestational age at birth compared with the group of spontaneous conception.

Table I Maternal and perinatal characteristics of the study groups.

	ART conception (n = 188)	Spontaneous conception (n = 1168)	P
Maternal baseline characteristics			
Age (years)	37.1 ± 3.8	36.4 ± 3.5	0.02
	37 (35–40)	37 (35–39)	
BMI (kg/m ²)	22.0 ± 3.2	22.1 ± 3.3	0.67
	21.3 (19.9–23.1)	21.5 (19.8–23.4)	
Previous miscarriage (1 or more)	42/188 (22.3%)	244/1168 (20.8%)	0.60
Non-European Union citizenship	15/186 (8.1%)	97/1137 (8.5%)	0.94
Perinatal outcome characteristics			
Gestational age at birth (weeks)	40.0 ± 1.2	40.1 ± 1.2	0.61
	40.1 (39.1–41.0)	40.1 (39.3–41.0)	
Cesarean section	42/188 (22.3%)	195/1168 (16.7%)	0.07
Epidural analgesia ^a	37/81 (45.7%)	168/438 (38.4%)	0.22
Episiotomy ^a	62/146 (42.5%)	372/973 (38.2%)	
Perineal tears > II degree ^a	15/91 (16.5%)	66/591 (11.2%)	0.20
Blood loss at birth (ml)	414 ± 279	292 ± 236	0.00
	400 (200–600)	200 (100–400)	
Birthweight (g)	3355 ± 415	3319 ± 416	0.19
	3345 (3053–3650)	3300 (3040–3600)	
5 min Apgar Score <7	0/188 (0.0%)	4/1168 (0.3%)	0.42
Arterial blood pH	7.27 ± 0.07	7.26 ± 0.08	0.29
	7.27 (7.23–7.32)	7.26 (7.21–7.32)	

Continuous variables are expressed as mean ± SD and median (interquartile range). Categorical variables are expressed as n (%).

^aAmong cases of vaginal delivery.

The statistical tests applied were Mann–Whitney test (for continuous variables) and Chi-square test (for categorical variables).

The two groups also had similar prevalence of previous miscarriage, non-European Union citizenship, CS, epidural analgesia, episiotomy and third or fourth degree perineal tears, whereas blood loss at birth was more abundant in the ART group (Table I). There was no case of maternal death. Concerning neonatal outcomes, no differences were observed between ART conception pregnancies and spontaneous ones (Table I).

Table II shows the crude and adjusted OR for pre-specified obstetric and perinatal outcomes according to the mode of conception. ART conception did not increase the risks of labor induction, 'in labor' CS, acute fetal distress or fetal hypoxemia. However, patients who conceived by ART and underwent labor induction had a higher risk of failed induction compared with the control group (adjusted OR 2.53, 95% CI 1.23–5.21). ART conception reduced the risk of prolonged labor, i.e. active labor phase longer than 4 h (adjusted OR 0.53, 95% CI 0.33–0.87). The ART group showed a higher risk of operative delivery (adjusted OR 1.40, 95% CI 1.01–1.95), retained placenta (adjusted OR 2.63, 95% CI 1.31–5.26) and PPH, i.e. blood loss more than 1000 ml (adjusted OR 2.86 95% CI 1.37–5.99) compared with the natural conception group (Table II). The difference related to postpartum bleeding remained significant even after repeating the analysis without cases of retained placenta.

Discussion

The present study compared birth outcomes between women with healthy singleton pregnancies conceived through ART procedures and

women who conceived naturally, matched by maternal characteristics. The results showed that singleton uncomplicated term pregnancies from ART conception have a higher risk of failed induction, retained placenta and PPH but no increased risk of acute fetal distress or fetal hypoxemia. To our knowledge, no previous study has evaluated a group of women exposed to ART excluding most of the confounding factors that affect perinatal outcomes. According to our results, birth and postpartum management in uncomplicated term ART pregnancies may require counseling women about the risk of placental retention with PPH, but patients may be reassured about the lack of additional risks to the neonate.

The prevalence of induced labor was similar between the two groups. An increased rate of labor induction in ART pregnancies has been reported, although mostly due to obstetric complications (Hayashi et al., 2012; Barnhart, 2013; Sun et al., 2014). In our cohort, the main indications for labor induction were prolonged rupture of membranes and late-term pregnancy; however, we found a higher risk of failed induction, may be due to a myometrial dysfunction (Vannuccini et al. 2016).

Concerning the mode of delivery, ART conception was a protection factor against prolonged labor while increasing the risk of operative (either vaginal or abdominal) birth. Altogether, these findings suggest that ART gestations might be more subject to medical interventions to accelerate delivery and avoid a prolonged labor. This fact cannot be ascribed to a greater probability of acute fetal distress in ART, at least

Table II Crude and adjusted odds ratios of adverse perinatal outcomes associated with ART conception versus spontaneous conception.

	ART conception (n = 188)	Spontaneous conception (n = 1168)	Crude OR (95% CI)	Adjusted OR (95% CI)
Induction of labor				
Yes	73	382	1.29 (0.94–1.78)	1.18 (0.85–1.65)
No	114	772		
Failed induction ^a				
Yes	14	34	2.43 (1.23–4.80)	2.53 (1.23–5.21)
No	59	348		
Prolonged labor (>4 h) ^b				
Yes	23	219	0.51 (0.31–0.84)	0.53 (0.33–0.87)
No	82	400		
Cesarean section in labor ^b				
Yes	19	149	0.85 (0.51–1.41)	0.88 (0.52–1.48)
No	146	968		
Operative delivery ^c				
Yes	51	318	1.12 (0.79–1.60)	1.40 (1.01–1.95)
No	114	799		
Retained placenta ^d				
Yes	12	33	2.58 (1.30–5.12)	2.63 (1.31–5.26)
No	131	929		
Postpartum hemorrhage (blood loss >1000 ml)				
Yes	11	28	2.67 (1.30–5.49)	2.86 (1.37–5.99)
No	136	924		
Acute fetal distress				
Yes	12	59	1.28 (0.68–2.43)	1.44 (0.75–2.76)
No	176	1109		
Fetal hypoxemia (arterial blood pH <7.10)				
Yes	3	22	0.82 (0.24–2.76)	0.87 (0.25–2.95)
No	130	777		

^aAmong cases of induced labor.^bAmong cases of spontaneous or induced labor.^cCesarean section or vacuum extractor.^dAmong cases of vaginal delivery.

Multivariable backward stepwise (conditional) logistic regression was used to calculate odds ratios (OR) and 95% CI for each outcome, adjusting for maternal age, BMI, nationality and gestational age at birth.

in our study population, since we found the same risk of acute fetal distress, fetal hypoxemia and emergency ('in labor') CS in both study groups.

Our results show that ART pregnancies had higher risks of retained placenta, requiring manual removal and of PPH. Previous studies demonstrated a higher incidence of PPH and placental disorders in ART gestation, mostly related to placenta previa (Healy et al., 2010; Rombauts et al., 2014; Kaser et al., 2015). In our cohort, all known placental pathologies were excluded, but a higher risk of placental retention in ART pregnancies was still registered. A recent pathology study analyzed the morphological characteristics of the placental basal plate in ART pregnancies, suggesting a possible association with an increase in the amount of bleeding in deliveries (Nakamura et al., 2015). There was a significantly higher mean thickness of Rohr fibrinoid layer and a higher percentage of loss of decidua in ART placenta,

correlating with the bleeding at birth. Probably, unidentified factors associated with determining the thickness of the Rohr fibrinoid layer may have indirectly-affected bleeding during placental separation. Moreover, hormonal treatments in early pregnancy may cause changes in the structure and/or function of the extracellular matrix in the decidua layer, as represented by the percentage of loss of decidua, and thereby contributing to an association with increased bleeding in deliveries (Nakamura et al., 2015). Thus, events around the time of implantation may induce suboptimal endometrial function as a critical mechanism (Vannuccini et al., 2016). High oestradiol and progesterone concentrations, as a result of multiple folliculogenesis, may produce suboptimal angiogenesis and placentation, predisposing to PPH. Therefore, a major role may be played by ART procedures themselves, but uterine and hormonal conditions associated with infertility may contribute to the increased failed induction and postpartum

complications observed (Stern et al., 2015; Healy et al., 2010; Aziz et al., 2015).

Concerning neonatal outcome, we observed that term newborns from ART gestation had the same weight as naturally conceived counterparts and also the same risk of perinatal hypoxemia. A recent report on a large US IVF database showed that infants born from ART have a similar birthweight compared with spontaneously-conceived ones, suggesting that intrauterine growth is not reduced in singleton IVF babies (Dickey et al., 2016). Our present findings in full-term infants further suggest that ART conception does not increase the risk of perinatal hypoxemia, despite the possibly increased risk of abnormal placentation.

Gynecological conditions, such as PCOS, uterine fibroids and endometriosis, were excluded from our study population, but our database lacked specific information about causes of infertility, smoking habit and family income, limiting in part our results. In addition, a potential under-reporting of ART or incorrect information about the type of fertility treatment may have biased results, misclassifying the exposed and unexposed. The dataset lacks also specific information about the type of technique used (IVF or ICSI) and whether it was a fresh or a frozen cycle. Another limitation to acknowledge is a reduced generalizability of study findings to all nations and settings, as the data refer to well-resourced obstetric facilities in a high-income economy country. However, one of the strengths of the study is the strict inclusion criteria that allowed us to analyze a homogenous population and obtain more reliable results. In fact, only autologous IVF/ICSI pregnancies were included, in order to remove the bias related to conception by oocyte/embryo donation. In addition, the inclusion of only uncomplicated pregnancies until the onset of labor provides a well-defined and still largely representative population sample.

In conclusion, pregnancies conceived by autologous IVF or ICSI and managed in well-resourced obstetric facilities, even if uncomplicated until birth, have a higher risk of failed induction, retained placenta and PPH. Thus, patients should be counseled about the risk of peripartum and postpartum complications in the case of ART conception. Obstetricians often need to offer counsel about birth plans to this group of pregnant women, who are mostly nulliparous with advanced maternal age and become pregnant after years of infertility. The clinician's role should be to provide the best evidence-based counseling to the pregnant woman for a better management of the birth, and postpartum. This observation has implications not only for counseling, but also in terms of health services and health policies. In fact, this group of women should be considered as an 'at risk' category, and thus preventative strategies should be applied for postpartum management. However, sufficient evidence to support specific medical interventions to prevent these complications is still lacking. This is mostly because of a paucity of studies investigating the underlying pathogenetic mechanisms that explain the increased risk of these complications in ART pregnancy.

Therefore, further studies are needed in order to investigate the potential endometrial or myometrial factors implicated in the pathogenesis of peripartum and postpartum complications in pregnancies conceived by ART.

Authors' roles

SV, CF, MDT and FP developed the study design. CF, FP and SP contributed to data collection and management. SV, FMR and CF

performed the statistical analysis. All authors contributed substantially interpretation of data. SV wrote the first draft of the manuscript. All authors contributed to redrafting of the manuscript. MDT, FP, FMR and FMS revised critically the manuscript for important intellectual content. All authors approved the final submitted version.

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Conflict of interest

The authors report no conflict of interest.

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