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The PLART study: incidence of preterm labor and adverse pregnancy outcomes after assisted reproductive techniques—a retrospective cohort study

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Abstract

Key message **Even though assisted reproductive techniques represent one of the greatest achievements in modern medicine, the risk of preterm birth related to these pregnancies is about twice as high. This must be highlighted and further investigated to optimize the management of both mothers and newborns.**

Purpose The purpose of this study was to compare adverse pregnancy outcomes after assisted reproductive techniques (ART) and spontaneous conceptions, focusing on the incidence of preterm births (PTB) and distinguishing between iatrogenic and spontaneous events.

Methods This retrospective cohort study analyzed single births of one Italian hospital. The incidence of PTBs in ART pregnancies, divided into iatrogenic procedures, spontaneous preterm labors and preterm premature ruptures of the membranes (pPROMs), was compared with the non-ART control group. The incidence of other adverse pregnancy outcomes and the types of delivery were also reported and compared.

Results Of the 11,769 single births included, 2.39% were conceived by ART. The incidence of PTBs was 4.74% for spontaneous pregnancies and 12.8% for ART pregnancies (aOR 1.93; 95% CI 1.29–2.88). The percentage of iatrogenic procedures was 27.78% in the ART-PTBs' group and 30.88% in the non-ART-PTBs' controls. ART pregnancies showed an increased incidence of pPROMs (6.40% versus 2.41%), preterm labors (2.85% versus 0.93%), hypertensive disorders of the pregnancy (8.19% versus 2.32%), placenta previa (3.20% versus 0.59%), cesarean sections (28.47% versus 16.27%) and vacuum extractions (10.32% versus 5.19%).

Conclusions Singleton ART pregnancies have a higher risk of PTB which is mostly linked to a higher incidence of pPROMs and spontaneous preterm labor. The concurrency of a demonstrated higher risk of hypertensive gestational disorders and placenta previa suggests that placental development plays an important role in the pathogenesis of PTB.

Keywords Assisted reproductive techniques · Preterm birth · Preterm labor · Preterm premature rupture of membranes · Gestational hypertension · Placenta previa

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Abbreviations

APO	Adverse pregnancy outcome
ART	Assisted reproductive techniques
BMI	Body mass index
PLART	Preterm labor after assisted reproductive techniques
PTB	Preterm birth
pPROM	Preterm premature rupture of the membranes

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Introduction

Pregnancy from assisted reproductive techniques (ART) has become an increasing challenge for obstetricians. Undoubtedly ART help infertile couples achieving pregnancy, but they also represent a raising public health challenge. In fact, the association between ART and adverse birth outcomes, such as preterm birth (PTB) and low birth weight has been reported [1, 2].

Lately, a new concept defined with the acronym APOs (adverse pregnancy outcomes) is being developed in the literature [3]. This definition groups together a series of adverse obstetric events that are believed to have the same etiopathogenetic origin. In particular, it refers to the restriction of growth in utero (IUGR), hypertensive disorders of pregnancy and preeclampsia, preterm birth, abruptio placentae and preterm premature rupture of the membranes (pPROMs). In fact, it appears that the first etiopathogenetic *movens* is a defective trophoblastic invasion in the first trimester, from which an aberrant placentation would arise in the second trimester.

The etiology of APOs in ART pregnancies is yet unclear. Many hypotheses have been formulated, like gametes' and embryos' manipulation, laboratory conditions during embryos' culture, culture medium, as well as the use of fertility medications [4]. Certainly, in most cases, a deep anxiety both of the mother and the gynecologist is possibly linked to an increased number of pregnancy checkups and iatrogenic procedures. Moreover, it is important to understand that subfertility itself represents an independent risk factor for APOs [5–7].

A non-standardized obstetrical approach to these patients and the different medical management among countries require a clear picture to establish a common "good-practice" approach.

In Italy, more than 13,500 babies born in 2016 were conceived by ART, and they represent 2.9% of all newborns (89% with autologous ART and 11% with heterologous ART) [8].

The main goal of this study was to evaluate the rate of preterm birth in an Italian referral ART center, distinguishing between iatrogenic and spontaneous PTBs, among ART pregnancies compared to the spontaneous ones. Secondarily, we further explored the rate of placental defects and hypertensive disorders of pregnancy among the two groups, assuming that these pathologies share a common etiology with PTB.

Materials and methods

The preterm labor after assisted reproductive techniques (PLART) is a single institution cohort study that investigates the risk of preterm labor and other adverse pregnancy outcomes as a result of different ART techniques, compared to pregnancies with spontaneous conception. The cohort is composed by all births that took place in the Hospital of Rimini between January 2014 and March 2018. The log-80web1.auslrn.net software was used to identify all women that delivered in the Hospital of Rimini in the study period. All medical records have been reviewed by two investigators to select the eligibility criteria.

Exclusion criteria were: twin pregnancies and vanishing twins (defined by the resorption of one fetus in a twin pregnancy), stillbirths (defined by babies born with no sign of life), and severe congenital malformations (such as severe cerebral and gastrointestinal malformations and known trisomies). According to some authors, the prevalence of extremely preterm delivery rate is higher in the vanishing twin syndrome group, with a pooled risk ratio of 3.5 (1.72, 7.12) [9]. Since we aimed to conduct a study on singleton births, it was decided to exclude twin pregnancies and the vanishing twin syndromes, assuming that they could represent a confounding bias for PTB.

ART pregnancies were identified and divided between autologous techniques and heterologous techniques. The remaining patients with spontaneous conception constituted the control group for the study. Socio-demographic features and clinical characteristics were recorded. The incidence of preterm birth was studied for each group and assessed if due to a medical indication or a spontaneous event, either after a pPROM or after the onset of a spontaneous labor. PTBs were defined when occurring at less than 37 weeks of gestation (until 36 weeks + 6 days). In the iatrogenic PTB's group, we included all deliveries before 37 weeks of gestation, in which labor was either induced or the infant was delivered by pre-labor cesarean section, either for maternal or fetal indications.

The incidence of other adverse pregnancy outcomes, such as hypertensive disorders of pregnancy, placental defects and placental abruption, and the type of delivery (vaginal birth, cesarean section or vacuum extraction) were recorded.

Descriptive and univariable analyses were used. Statistical tests used for univariate analysis were: Chi-squared test, Student's *t* test and Mann–Whitney test. Analyses were two-tailed and p values < 0.05 were considered statistically significant. Logistic regression models were used to calculate the odds ratio (OR) and corresponding 95% confidence intervals (CI) for PTB in the ART population. Models were adjusted for maternal age, hypertensive disorders, parity and history of a previous PTB. All analyses were performed using the statistical software package STATA /SE 14.2 for windows.

The study size was calculated considering PTB as primary outcome: estimating that the incidence of PTB in the general population is 5–6% and that its expected incidence in ART pregnancies is about 10%, and estimating a relationship between ART pregnancies and spontaneous pregnancies of 1:50 (2%), a sample of 15,000 births was needed to obtain a power of 90% with alpha error 0.05.

All data were collected and analyzed keeping anonymity, according to European laws on privacy. The study was approved by the Local Ethics Committee (Comitato Etico di Area Vasta Romagna) in February 2018.

Results

The study included 11,769 single births that met the eligibility criteria, out of the 12,056 births occurred in Rimini between January 2014 and March 2018 examined for eligibility. The number of single pregnancies obtained by ART was 281 (2.39% of the overall population), 232 of them following autologous techniques (82.56%) and 49 following heterologous techniques (17.44%), as reported in Fig. 1.

Socio-demographic and clinical characteristics of the study population are shown in Table 1. Women with ART pregnancies were older and more often nulliparous than controls, as expected. The majority of ART-treated women had Caucasian ethnicity and Italian nationality. ART-treated women were less likely to smoke than the control group. The BMI mean value and the percentage of women with a history of a previous PTB did not differ significantly between the two groups.

Table 2 shows the rate of PTBs in the study population, distributed by type of conception and type of ART. The incidence of PTBs in spontaneous pregnancies was 4.74%, while the incidence of PTBs in the study's ART population was 12.8% (12.5% in case of autologous ART and 14.29% in case of heterologous ART) with a p value < 0.001. Considering the causes of PTBs in the two groups, the incidence of iatrogenic PTBs was 30.88% in spontaneous pregnancies and 27.78% in ART population (not significant). The pPROM rate was 6.40% in the ART population versus a rate of 2.41% in spontaneous pregnancies (p value < 0.001), and the rate of spontaneous preterm labor was 2.85% in ART population versus a rate of 0.93% in spontaneous pregnancies (p value < 0.001).

The crude odds ratio (cOR) for PTB in the study's ART population was 2.77 with a 95% confidence interval (95% CI) of 1.92–4.01. Since maternal age, hypertensive disorders of the pregnancy, nulliparity and history of a previous PTB were positively associated with the rate of PTBs, data were adjusted for these four confounding variables. The resulting adjusted odds ratio (aOR) for PTB in the study's ART population was 1.93, with a 95% CI of 1.29–2.88. The post hoc power analysis showed that, considering the primary outcome, the study achieved a power of 91%, with 0.05 alpha error.

In Table 3, the type of birth and the rate of APOs are compared between ART and non-ART women. ART pregnancies were associated with an increased rate of cesarean sections (28.47% versus 16.27%) and a doubled incidence of vacuum extractions (10.32% versus 5.19%). We need to specify that the 16.27% rate of cesarean sections in the non-ART study group is a very particular situation of the

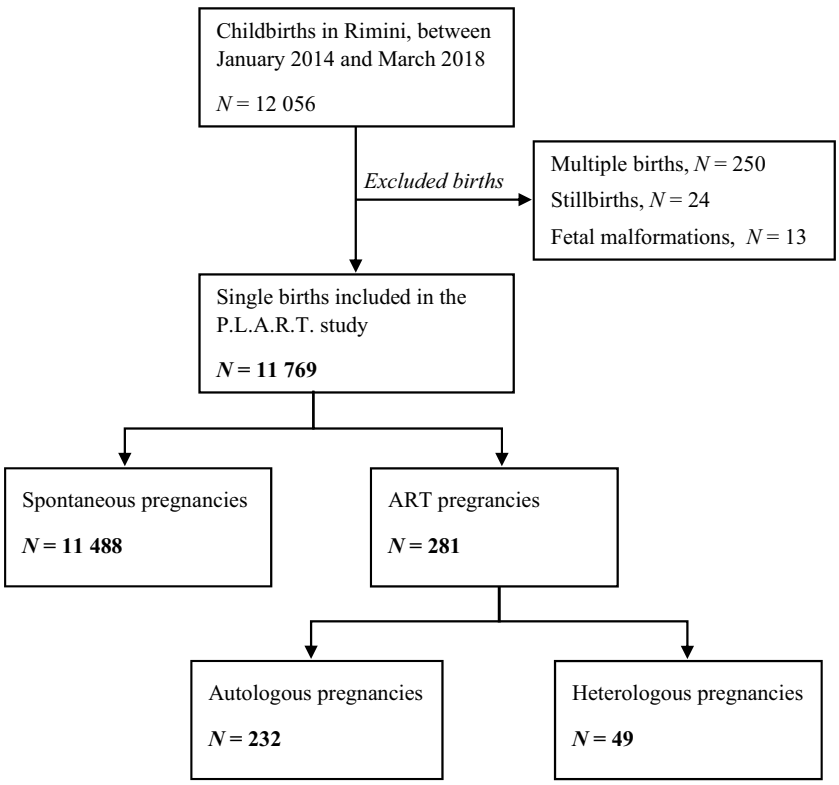

Fig. 1 Flow chart of the study population—the preterm labor after assisted reproductive techniques cohort

Table 1 Maternal socio-demographic and clinical characteristics of the study population

	ART *N* = 281	No ART *N* = 11 488	Univariable analysis
Maternal age, years			$p < 0.001$
Mean (SD, range)	37.54 (± 5.33, 22–51)	31.95 (± 5.47, 15–49)	
Maternal age class, *N* (%)			$p < 0.001$
≤ 30 years	27 (9.61)	4414 (38.44)	
31–40 years	177 (62.99)	6487 (56.49)	
≥ 41 years	77 (27.40)	582 (5.07)	
BMI, kg/m^2			$p = 0.059$
Mean (SD, range)	22.52 (± 3.92, 16.3–38.67)	23.03 (± 4.36, 15.7–55.47)	
Smokers, *N* (%)			$p = 0.016$
Yes	29 (14.22)	1836 (21.20)	
No	175 (85.78)	6823 (78.80)	
Not specified	77 (–)	2829 (–)	
Ethnicity, *N* (%)			$p = 0.011$
Caucasian	268 (95.37)	10,268 (89.38)	
African	5 (1.78)	657 (5.72)	
Latino-American	4 (1.42)	257 (2.24)	
Asian	4 (1.42)	306 (2.66)	
Nationality, *N* (%)			$p = 0.001$
Italian	224 (79.72)	8090 (70.42)	
Not Italian	57 (20.28)	3398 (29.58)	
Parity, *N* (%)			$p < 0.001$
Nulliparous	232 (82.56)	6149 (53.53)	
Parous	49 (17.44)	5339 (46.47)	
Previous PTB, *N* (%)			$p = 0.398$
Yes	6 (2.14)	348 (3.03)	
No	275 (97.86)	11,140 (96.97)	

Values are numbers *N* (%) or mean (± standard deviation, range)

ART assisted reproductive techniques, *BMI* body mass index, *PTB* preterm birth

Table 2 Preterm rate in the preterm labor after assisted reproductive techniques cohort

	ART—autologous *N* = 232	ART—heterologous *N* = 49	No ART *N* = 11 488	Univariable analysis
Term, *N* (%)	203 (87.50)	42 (85.71)	10,944 (95.26)	
Preterm, *N* (%)	29 (12.50)	7 (14.29)	544 (4.74)	$p < 0.001$
After pPROM	18 (50.00[a])		269 (49.45[a])	
Preterm labor	8 (22.22[a])		107 (19.67[a])	
Medical indications	10 (27.78[a])		168 (30.88[a])	

Values are numbers *N* (%). Medical indications stand for induction of labor or pre-labor cesarean section before 37 weeks

ART assisted reproductive techniques, *pPROMs* preterm premature rupture of the membranes

[a]Percentage of the preterm group.

Hospital of Rimini, which is one of the top three Gynecology and Obstetrics Units with the lowest cesarean section rate in Italy. The increased risk for operative deliveries in the ART group, both with cesarean section and vacuum delivery, was significantly higher with a p value < 0.001.

Moreover, there was a significative association between ART and increased rate of hypertensive disorders of pregnancy (8.19% versus 2.32%) and placenta previa (3.20% versus 0.59%). No significative difference was found in the

Table 3 Obstetric outcomes in the preterm labor after assisted reproductive techniques cohort

	ART $N=281$	No ART $N=11\,488$	Univariable analysis
Type of birth, *N* (%)			$p<0.001$
Vaginal birth	172 (61.21)	9023 (78.54)	
Cesarean section	80 (28.47)	1869 (16.27)	
Vacuum extraction	29 (10.32)	596 (5.19)	
Hypertensive disorders	23 (8.19)	267 (2.32)	$p<0.001$
Gestational hypertension	16 (5.69)	206 (1.79)	
Preeclampsia	6 (2.14)	54 (0.47)	
Eclampsia	1 (0.36)	3 (0.03)	
HELLP syndrome	0 (0.00)	4 (0.03)	
pPROMs	18 (6.40)	277 (2.41)	$p<0.001$
Placental defects	9 (3.20)	72 (0.63)	$p<0.001$
Placenta previa	9 (3.20)	68 (0.59)	
Vasa previa	0 (0.00)	4 (0.03)	
Placental abruptions	1 (0.36)	32 (0.28)	$p=0.809$

Values are numbers *N* (%)

ART assisted reproductive techniques, *pPROMs* preterm premature rupture of the membranes, *HELLP* hemolysis, elevated liver enzymes, low platelets

incidence of vasa previa and placental abruption between the ART group and the controls.

Discussion

According to literature [10–14], the results of this study show an increased risk of PTB in pregnancies obtained through ART, compared to the spontaneous ones. The PLART study, for the first time, further investigates in two subgroups the percentages of iatrogenic preterm deliveries, spontaneous preterm labor with intact membranes, and pPROMs. As a result, we found that the percentage of fetal and maternal indications that led to iatrogenic PTBs (either inductions of labors or pre-labor cesarean sections) in the ART group was not higher than in the spontaneous pregnancies group.

Therefore, the higher risk of PTBs in this ART population was not due to an increased number of medical indications to end the pregnancy, but was related to an increased percentage of spontaneous preterm labors and pPROMs. This suggests an intrinsic risk that could be related to an abnormal placentation, and this is supported by the evidence of hypertensive disorders during pregnancy and an increased risk of abnormal site of placentation (placenta previa).

This study supplies increasing evidence that pPROMs and spontaneous preterm labor share a biological etiology with other APOs. Pathways implicated in the etiology of pPROMs include hematological/coagulation function disorder, collagen metabolism, matrix degradation and local inflammation [15, 16]. The high rate of pPROMs in the ART population may suggest the activation of one of these pathways.

While an increased risk of cesarean sections was already reported in the literature [14], we found that the rate of operative vaginal extractions was also increased. These results could be related to an alteration in the second stage of labor leading to a dystocic labor. However, the interpretation of our findings needs to be supported by further studies, exploring the length of labor in these pregnancies.

The evaluation of the differences between autologous and heterologous ART pregnancies could not be conclusive as the numbers are scanty. This is due to the fact that, in Italy, ovodonation is not yet common, but an emerging reality, making it difficult to collect a wide number of cases.

The PLART study has some limitations, such as its retrospective design, that made it not possible to collect data on the causes of infertility and hormonal protocols used in each ART case, nor on the reasons that lead to an operative delivery.

Nevertheless, the PLART study has several strengths. First of all, it is the first Italian study that collected data from a large cohort of patients, showing the demographic features and obstetric outcomes of the local ART pregnancies, providing robust statistics. Moreover, we collected data from a single obstetric department, so that the outcomes were not affected by different obstetric managements or protocols.

Conclusion

The management of ART pregnancies requires dedicated counseling and follow-up that take into account their twofold risk for PTB and their higher rate of hypertensive disorders and placental defects. The etiology of this group of pathologies must be further investigated focusing on the placental development.

An adequate counseling must highlight these risks to the mothers and offer a closer follow-up.

Lastly, the increased incidence of cesarean sections and vacuum extractions suggests that ART pregnancies are associated with a dystocic second stage of labor. This association needs to be explored further with dedicated studies on the mechanisms that could lengthen labor.

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Author contributions We certify that all authors equally contributed to the realization of the study. In particular: AC data collection. PG, FS and BT project development. GN manuscript writing. ES data collection and manuscript writing. MS manuscript editing.

Compliance with ethical standards

Conflict of interest All authors declare that there is no conflict of interest.

Ethical approval Given its retrospective design, this article does not contain any studies with human participants or animals performed by any of the authors. All data were collected and analyzed keeping anonymity, according to European laws on privacy. The study was approved by the Local Ethics Committee (Comitato Etico di Area Vasta Romagna) in February 2018. According to the Italian Authorisation of the Guarantor n.9/2016 and taking into account the logistic impossibility to reach out to all the women included in the study, given the large number of the sample, the investigators were exonerated from the request of informed consents.

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