Journal of Gynecology Obstetrics and Human Reproduction 48 (2019) 845–848

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Original Article

Influence of assisted reproductive technologies on maternal and neonatal outcomes in early preterm deliveries

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ARTICLE INFO

Article history:
Received 25 December 2018
Received in revised form 25 February 2019
Accepted 15 March 2019
Available online 18 March 2019

Keywords:
ART (assisted reproductive technologies)
Spontaneous conception
IVF (in vitro fertilization
Early preterm birth
Fetal outcome
Maternal outcome

ABSTRACT

Introduction: Compared to spontaneous conception (SC), pregnancies conceived through assisted reproductive technologies (ART) carry worse pregnancy and neonatal outcomes. Evidences focused on preterm births are limited. Early preterm delivery is a critical situation for medical management and parental counselling. The aim of this study was to analyze if ART procedures influenced pregnancy and neonatal outcomes in singleton pregnancies with early preterm delivery.

Material and methods: This was a retrospective case control study. The population consisted of all consecutive early preterm deliveries occurred at Careggi University Hospital in Florence (Italy) between 2010 and 2017. Cases were considered patients who conceived though ART, including intra cytoplasmic sperm injection (ICSI), in vitro fertilization and embryo transfer (IVF-ET), intra uterine insemination (IUI) and ovarian stimulation. Controls were patients who conceived in the natural way.

Main outcomes of the study were: birth weight, umbilical artery pH, Apgar score at 1 and 5 min, gestational age at delivery and mode of delivery.

Secondary outcomes were: spontaneous preterm labor initiation, gestational diabetes mellitus, intrauterine growth restriction (IUGR), cholestasis of pregnancy, intra uterine fetal demise (IUFD), placenta previa, fetal malformations, pregnancy induced hypertensive (PIH) disorders (gestational hypertension, preeclampsia and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome) and postpartum hysterectomy.

Shapiro-Wilk test was used to check the normality of the data; Mann-Whitney test was used to compare two continuous variables not-normally distributed. Multiple and binomial logistic regression analyses were used to adjust the results of the statistical analysis for potential confounding factors. The analysis for the main outcomes was performed for all deliveries and then repeated for spontaneous deliveries, separately.

Results: Seventy-one patients had ART and 640 SC. We found no differences in birthweight, umbilical artery pH, Apgar at 1 and 5 min and gestational age at delivery between ART and SC groups. C-section rate, placenta previa and PIH disorders were higher in the ART group. The higher prevalence of C-sections in the ART group was not statistically significant after adjusting for age and parity in the whole population but resulted significantly different when analyzing the subgroup of patients with spontaneous initiation of labor.

Conclusions: Fetal outcomes seem to be equal between ART and SC in early preterm neonates ; C-section rate and pregnancy complications such as placenta previa and PIH disorders seem to be higher in the ART group. These information should be part of the family counselling in these cases. We suggest that clinicians, after management of preterm delivery had been properly addressed, should not apply different management in ART compared to SC pregnancies.

1. Introduction

Millions of babies are born trough assisted reproductive technologies (ART) : 1–5% of all the newborns in developed countries is conceived through ART [1,2]. Compared to

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http://dx.doi.org/10.1016/j.jogoh.2019.03.008
2468-7847/

spontaneous conception (SC), pregnancies conceived through ART carry worse maternal and neonatal outcomes [3,2].

The risks derive from the high technology treatment itself, but also from the baseline clinical and biological risk factors present in a selected group of infertile patients. Indeed, the infertility state is often linked to many preconception risk factors [4].

Fetal outcomes in ART are largely influenced by the presence of twins, in fact more than 20% of babies born through ART in the United States (US) are twins [5]. Worse outcomes are usually seen with twins, but also singleton pregnancies conceived through ART are affected, in particular by higher rates of preterm birth (PTB) and low birthweight, compared to SC [6].

Most of the current research has been devoted to multiple pregnancies [6], nonetheless in singletons, several systematic reviews and meta-analysis have reported an increased risk of PTB, antepartum hemorrhage, pregnancy-induced hypertension, pre-eclampsia, gestational diabetes mellitus, C-section, low birth weight, placenta previa, placenta abruption, postpartum hemorrhage, small for gestational age, peripartum hysterectomy, admission to neonatal intensive care unit, and perinatal mortality in ART-conceived pregnancies compared to SC [7].

In a recent meta-analysis of singleton pregnancies [8] Cavoretto et al. compared 8044 IVF to 53633 SC and showed a significant increase in the incidence of PTB < 37 weeks (OR 1.75) and PTB < 34 weeks (OR 1.78).

A recent study [9] analyzed the relationship between in vitro fertilization (IVF) and neonatal outcomes in very low birth weight preterm infants born at <=32 weeks, with no detectable relationship with neonatal outcomes.

One previous study compared neonatal outcomes between preterm deliveries (<35 weeks) conceived trough IVF to SC and found no major differences in neonatal outcomes, but they did not adjust the analysis for age and parity and they did not specify the IVF-technique used [10].

In the critical situation of early preterm delivery, doctors and patients are in front of challenging decisions and the contribution of ART to the maternal and neonatal well-being has been questioned.

The aim of this study was to analyze if ART procedures influenced maternal and neonatal outcomes in singletons with early preterm delivery.

2. Material and methods

This was a retrospective case control study. The population consisted of all consecutive singleton early preterm deliveries occurred at Careggi University Hospital in Florence (Italy) between 2010 and 2017. Early preterm delivery was defined according to the Eunice Kennedy definition, considering babies delivered before 34 weeks of pregnancy [11]. Gestational age was calculated from the last menstrual period and was confirmed by fetal crown–rump length measurement at the first trimester ultrasound [12]. Cases were considered patients who conceived trough ART, including intra cytoplasmic sperm injection (ICSI), in vitro fertilization and embryo transfer (IVF-ET), intra uterine insemination (IUI) and ovarian stimulation. Recent data indeed highlighted that not only ICSI and IVF-ET [7], but also IUI and ovarian stimulation [13] carry a risk of adverse prenatal outcomes. Patients who were oocyte recipients were included in the group of cases. Controls were patients who conceived in the natural way.

Demographics were recorded as follows: age, BMI, smoking (current/history), parity, gravidity, cause of infertility.

Main outcomes were the following: birthweight, umbilical artery pH, Apgar score at 1 and 5 min, gestational age at delivery, mode of delivery.

Secondary outcomes were: spontaneous vs iatrogenic initiation of labor/iatrogenic delivery, gestational diabetes mellitus, intrauterine growth retardation (IUGR), cholestasis of pregnancy, intrauterine fetal demise (IUFD), placenta previa, fetal malformations, pregnancy induced hypertensive (PIH) disorders (gestational hypertension, preeclampsia, hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome), postpartum hysterectomy. IUGR was defined when the estimated fetal weight by sonogram was less than 10th percentile [14].

Statistical analysis was performed with SPSS v. 22.0 (IBM, Chicago, US).

Continuous variables were expressed with median [25°-75^{0}percentile]; categorical variables were indicated by percentage.

We assessed the normality of data with the Shapiro-Wilk test: all the variables had a p-value below 0.05, indicating that all the data significantly deviated from a normal distribution.

To compare the demographics and outcomes variables between the cases (ART) and controls (SC), we used the non-parametric Mann-Whitney test. To compare the categorical variables we used the Chi-square test.

In addition to the univariate analysis, we performed also a multivariate model analysis to adjust the results for the confounding factors age and parity. We used a multiple regression analysis when the dependent variable was continuous and a binomial logistic regression analysis when the outcome was dichotomic. A p-value of less than 0.05 was considered statistically significant.

3. Results

A total of 711 patients matched the inclusion criteria and were enrolled in the study: the median age was 33 [29–37] years old; median BMI was 22.6 [20–36] kg/mt^2, 414/711 (58%) were nulliparous and 1% smokers.

Seventy-one had ART and 640 SC (Fig. 1). In the ART group, 35 had IVF-ET, 27 had ICSI, 5 had medical ovarian stimulation and 4 had IUI; 16 patients were egg donor recipients, of which 8 had ICSI and 8 had IVF-ET.

The causes of infertility were distributed as follows: ovulatory factor 17%, utero-tubal factor 25%, male factor 26%, 25% had a combination of factors and 7% did not show any definitive alteration on the performed diagnostic tests.

Age, parity and gravidity were significantly different between the 2 groups (Table 1).

Out of the 640 participants, 445 had a spontaneous initiation of labor, of which 40 had ART and 405 SC (Fig. 1).

C-section rate was 66% in the whole population and 46% on the patient with spontaneous initiation of labor; the most frequent indications for C-section were IUGR 93/471 (20%), non-reassuring fetal heart rate (NRFHR) 57/471 (12%), preeclampsia 48/471 (10%), placenta abruptio 41/471 (9%), previous C-section 22/471 (5%).

The total 6 postpartum hysterectomies were performed for uterine atony/hemorrhage right after the delivery.

We found no differences in birthweight, umbilical artery pH, Apgar at 1 and 5 min, gestational age at delivery between ART and SC groups (Table 2). The C-section rate was higher in the ART group compared to the SC group (p = 0.018). This difference was not statistically significant after adjusting for age and parity in the whole population but resulted significantly different when analyzing the subgroup of patients with spontaneous initiation of labor (Table 3).

Among pregnancy-related disease, only placenta previa and PIH disorders were more prevalent in the ART group (Table 1).

4. Discussion

C-section rate, placenta previa and PIH disorders resulted significantly higher in ART vs SC. All the other neonatal and maternal outcomes were comparable in the two groups.

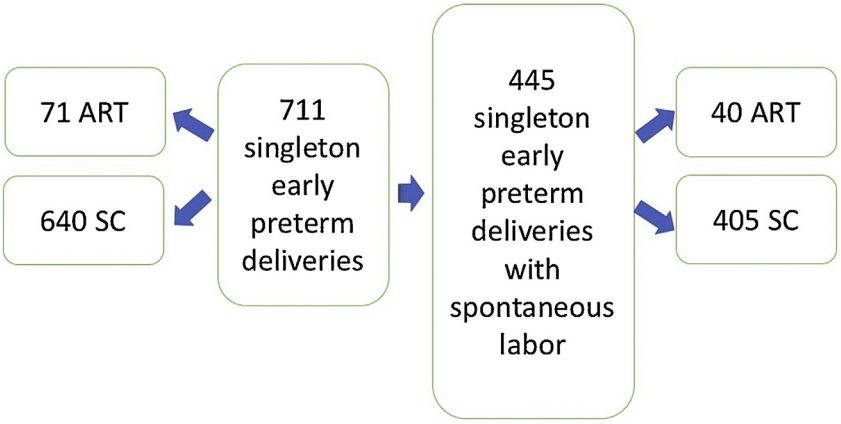

Fig. 1. Summary of case and control groups. ART: Assisted Reproductive Technologies; SC: spontaneous conception.

Table 1
Demographics. ART: Assisted Reproductive Technologies; SC: Spontaneous Conception; BMI: Body Mass Index. Continuous variables are expressed with median [25°-75° percentile]; categorical variables are expressed with ratio and percentage out of the total.

	ART(n = 71)	SC (n = 640)	P value	P value
Age (years)	38 [34.5–42.5]	33 [29–37]	<0.001*	
BMI (Kg/mt^2)	22.9 [21–26.2]	22.6 [20.2–26]	NS*	NS***
Smoking (current/past)	1 (1%)	5 (1%)	NS**	NS***
Parity > 0	6/71 (8%)	291/640 (45%)	<0.001**	
Gravidity > 1	25/71 (35%)	405/640 (63%)	<0.001**	

* Mann-Whitney test.
** Chi-square test.
*** Multiple Regression Analysis, adjusted for age and parity.

The higher rate of C-sections was not confirmed in the whole population when adjusting for age and parity but remained significantly higher when considering the subgroup of patients who had a spontaneous initiation of labor.

Overall, the C-section rate was high: 66% in the whole population and 46% on the patient with spontaneous initiation of labor: the clinicians in our clinic maintain a low threshold for C-section probably out of fear of legal litigations, but an actual verification of this data resulted impossible.

Other studies have found a lack of association between infertility and C-section after adjusting for maternal age [15] but our is the first study analyzing a subgroup of patient with spontaneous initiation of labor.

We speculate that ART patients may have a higher rate of dysfunctional labor which requires operative deliveries to maintain neonatal outcomes comparable with the SC group, but further studies are needed to confirm this hypothesis.

Placenta previa occurred more commonly in ART vs SC. Placenta-related complications have been recorded in previous studies [16]. The real biological reason is still a matter of debate, but current studies speculate that artificial manipulation of the gametes can lead to epigenetic modifications [17] and abnormal material exchanges at the maternal-fetal interfaces [16].

PIH disorders were more frequent in ART vs SC pregnancies. The association between PIH and ART has been confirmed by numerous studies: the exact mechanisms are elusive, but the main hypothesis is related to failed placentation systems, especially when considering ICSI and IVF-ET [18,16]. One previous study examined the influence of IVF on neonatal outcomes in very low birth weight preterm infants at <=32 weeks and found no differences [9].

Similarly to ours, a previous study compared neonatal outcomes between preterm deliveries (<35 weeks) conceived by in vitro fertilization (IVF) to SC and found no differences in neonatal outcomes, with the exception of bronchopulmonary dysplasia [10]. Differently from our study, they did not adjust the results for age/parity and they did not specify the IVF-techniques used, in

Table 2
Neonatal and pregnancy outcomes in whole population. ART: Assisted Reproductive Technologies; SC: Spontaneous Conception; GA: Gestational Age. Continuous variables are expressed with median [25°–75° percentile]; categorical variables are expressed with ratio and percentage out of the total.

Whole population	ART (n = 71)	SC (n = 640)	P value	P value
Neonatal weight (gr)	1360 [945–1810]	1335 [876–1830]	NS*	NS***
Umbilical artery pH	7.33 [7.28–7.36]	7.31 [7.26–7.36]	NS*	NS***
Apgar I minute	7 [6–8]	7 [6–8]	NS*	NS***
Apgar V minutes	9 [8,9]	8 [8,9]	NS*	NS***
GA at delivery (weeks)	30 [27–32]	30 [27–32]	NS*	NS***
C-section	56/71 (79%)	415/640 (65%)	0.018**	NS ****
Spontaneous initiation of labor	40/71 (56%)	405/640 (63%)	NS**	NS****
Postpartum Hysterectomy for uterine atony and hemorrhage	1/71 (1%)	5/640 (1%)	NS**	NS****
Gestational Diabetes Mellitus	9/71 (12%)	66/640 (10%)	NS**	NS****
Intrauterine Growth Restriction	16/71 (22%)	131/640 (20%)	NS**	NS****
Cholestasis of pregnancy	3/71 (4%)	7/640 (1%)	NS**	NS****
IUFD	0/71 (0%)	2/640 (0.3%)	NS**	NS****
Placenta Previa	8/71 (11%)	29/640 (4%)	0.015**	0.002****
Fetal Malformations	3/71 (4%)	25/640 (4%)	NS**	NS****
Pregnancy Induced Hypertensive disorders (Gestational Hypertension/Preeclampsia/HELLP)	20/71 (28%)	104/640 (16%)	0.012**	0.04****

* Mann-Whitney test.
** Chi-square test.
*** Multiple Regression Analysis, adjusted for age and parity.
**** Binomial logistic Regression Analysis, adjusted for age and parity.

Table 3
Pregnancy and fetal outcomes in spontaneous early preterm deliveries. ART: Assisted Reproductive Technologies; SC: Spontaneous Conception; GA: Gestational Age; IUFD: Intra Uterine Fetal Demise; HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelets. Continuous variables are expressed with median [25°-75° percentile]; categorical variables are expressed with ratio and percentage out of the total.

Spontaneous deliveries	ART (n = 40)	SC (n = 405)	P value	P value
Fetal weight (gr)	1725 [1075–1970]	1395 [865–1910]	NS*	NS***
Umbilical artery pH	7.34 [7.31–7.38]	7.33 [7.27–7.36]	NS*	NS***
Apgar I minute	7 [6–8.2]	7 [5–8]	NS*	NS***
Apgar V minutes	7 [6–8.2]	8 [8,9]	NS*	NS***
GA at delivery (weeks)	31 [26–32]	29 [26–32]	NS*	NS***
C section rate	26/40 (65%)	181/405 (44%)	0.014**	0.038****

* Mann-Whitney test.
** Chi-square test.
*** Multiple Regression Analysis, adjusted for age and parity.
**** Binomial logistic Regression Analysis, adjusted for age and parity.

addition, they did not mention the umbilical artery pH at delivery among the outcomes.

As mentioned above, in the literature is well established that ART is related to worse pregnancy and fetal outcomes [3]. In particular in singletons, ART is related to a more than double relative risk of preterm delivery [6].

The main strengths of our study are the selection of patient with early preterm deliveries, for which the available data are very limited, and the subgroup analysis of spontaneous preterm labor, for the first time in the literature to our knowledge.

The inclusion of IUI and ovarian stimulation among the cases is a strength of our study, considering the recent evidence of worse maternal and neonatal outcomes, when compared to SC [7].

Limitations of our study are the retrospective nature and the lack of subgroup analysis per different ART techniques or different C-section indications, because of the small number of samples available.

In general, the low number of cases provides the present study with a very low power to detect differences with the control group.

Another limitation of our study is the lack of some neonatal outcome measures such as length of stay in neonatal intensive care unit (NICU), neonatal mortality, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intra ventricular hemorrhage (IVH).

5. Conclusions

The majority of neonatal and maternal outcomes, after adjusting for age, parity and spontaneous/iatrogenic mode of delivery, seem comparable between ART and SC patients.

The lack of influence of the artificial mode of conception on neonatal outcome should be incorporate in the counselling given to parents of early preterm babies.

We suggest that clinicians, after management of preterm delivery have been properly addressed, should not apply different management techniques in ART vs SC babies.

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