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Twin pregnancies after assisted reproductive technologies: the role of maternal age on pregnancy outcome

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Twin pregnancies after assisted reproductive technologies: the role of maternal age on pregnancy outcome

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Abstract

Objectives: Our aim was to investigate whether advanced maternal age (≥40 years) still impairs the outcome of twin pregnancies after assisted reproductive techniques (ART).

Study design: The retrospective observational study evaluated 430 nulliparous dichorionic diamniotic twin pregnancies conceived with ART. The population was divided into women <40 years old (Group A, n=265) and ≥40 years old (Group B, n=165).

Results: Gestational diabetes mellitus and gestational hypertension/preeclampsia were significantly more frequent in nulliparous twin pregnancies after ART ≥40 years compared to <40 years (p=0.021 and p<0.001, respectively). In univariate analysis of twin pregnancies after ART, there was only a trend of higher incidence of total preterm birth (PB) rate within mother aged ≥40 years old (p=0.104). However, Group A showed higher rate of spontaneous preterm birth (SPB) <37 weeks, whereas Group B showed significantly higher rate of iatrogenic PB <37 weeks of gestation (p=0.023 and p=0.001, respectively). For delivery <32 weeks of gestation, the rate of SPB in Group A was significantly higher (p=0.002). A higher incidence of PB was observed in Group B after heterologous treatment (p<0.001). Despite this, the absolute prevalence of PB in the entire population is higher in Group A, both after autologous (22.5%) and heterologous (25%) ART treatment, than in Group B (10.1% vs 21.4%).

Conclusions: Our data indicate that nulliparous twin pregnancies conceived with ART in mothers ≥40 years old did not show significantly higher incidence of PB, even if an increased rate of iatrogenic PB <37 weeks is showed.

Keywords: twins, assisted reproductive technologies, maternal age, pregnancy outcome, preterm birth

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Introduction

The incidence of twin pregnancies has intensely increased and nowadays approximately 20% of deliveries following assisted reproductive techniques (ART) in Europe are twins[1]. The main contributor of this rising is represented by the increase in childbearing age postponing motherhood and the resulting increased use of ART for infertility treatment, and in particular the use of donor oocytes[1].

There is evidence that multiple gestation is associated with a higher risk of pregnancy-induced complications such as hypertension (PIH), preeclampsia (PE), and gestational diabetes (GDM), but also PB, antepartum and postpartum hemorrhage, cesarean delivery (CD), low birthweight (LBW) and increased perinatal mortality[2,3]. Several studies have shown that pregnancies after ART carry higher rates of pregnancy complications as compared to controls both in singleton or twin pregnancy such as PB, LBW and very LBW, fetal growth restriction (FGR), CD[4,5], birth defects, long-term sequelae and death[6]. Nevertheless, scientific data are still controversial and report similar or even better perinatal and neonatal outcomes[7].

Additionally, the contemporary trend of women of postponing pregnancy until after the third and fourth decades of life have resulted in an increased percentage of women undergoing the ART procedure at an advanced maternal age. Not only advanced maternal age has a significant negative impact on in vitro fertilization outcomes with low pregnancy and delivery rates (12.9% and 4.3%, respectively at 45 years of age)[8], but it has also been associated with an increased risk of obstetric and perinatal morbidity[9].

On this basis, the association of advanced maternal age, ART procedure and twin pregnancies could represent a combination of risk factors that may worsen the pregnancy and perinatal outcome.

The aim of this study is to investigate whether advanced maternal age (≥40 years) may impairs the outcome of twin pregnancies conceived with ART in nulliparous women.

Material and methods

This retrospective observational study evaluated 1141 multi-fetal deliveries that were managed at the Department of Obstetrics and Gynecology of the University of Siena, (Siena, Italy) and at the Department of Obstetrics and Gynecology of the University of Florence (Florence, Italy) from January 2010 to December 2014.

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With the aim to obtain a homogeneous population and to reduce the biases related to parity, type of ART treatment, triplets and monochorinicity, we applied specific inclusion and exclusion criteria (Figure 1).

The inclusion criteria were represented by nulliparity, dichorionic diamniotic (DCDA) twin pregnancies and ART conception. The exclusion criteria were multiparity, monocorial twin pregnancies, spontaneous conception and pregnancies conceived by ovulation induction and intrauterine insemination.

Based on these inclusion and exclusion criteria, the final study cohort included 430 deliveries of DCDA twin pregnancies conceived with ART. After inclusion, the population was divided into two groups considering maternal age <40 years old (Group A, n= 265) and ≥40 years old (Group B, n=165) (Figure 1).

Information about the obstetric and neonatal outcomes of the two groups was obtained from the women' hospital medical records and through questionnaires completed by a qualified obstetrician. For each pregnancy, the following maternal data were analyzed: maternal age and body mass index, nationality, type of conception (spontaneous conception or ART treatment), type of infertility treatment (autologous in vitro fertilization/intra-cytoplasmic sperm injection (IVF/ICSI), heterologous IVF/ICSI with oocyte or embryo donation), systemic diseases before pregnancy (pregestational hypertension, diabetes mellitus), diseases during pregnancy (GDM, PIH/PE, FGR, gestational hypothyroidism, intrahepatic cholestasis, preterm pre-labor rupture of membranes, PB, placenta abruption). As regards delivery and perinatal outcomes, the following data were recorded: gestational age at delivery, mode of delivery, spontaneous or iatrogenic preterm birth, neonatal birthweight at birth. Considering the iatrogenic preterm birth, maternal indications (uncontrolled pregestational hypertension or PIH/PE, uncontrolled diabetes mellitus or GDM, intrahepatic cholestasis, placenta abruption or previa, failed induction of labor) and fetal indications (FGR, breach presentation) to deliver were recorded.

Specific perinatal outcomes were not analyzed to avoid biases related to different management protocols applied in the two recruitment centers. Moreover, considering the retrospective design of the study, data regarding hematologic parameters (i.e. hemoglobin, platelet count, liver and renal function parameters), specific ultrasound data (i.e. estimated fetal weight, uterine and fetal doppler evaluation) and maternal post-partum data are excluded.

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The main outcome measure was represented by the occurrence of pregnancy complications, while secondary outcome measures were the association with pre-gestational diseases and type of infertility treatment.

Gestational age was calculated from the date of embryo transfer for ART pregnancies. GDM was diagnosed based on a 2-h 75-g oral glucose tolerance test. Hypertensive disorders were defined as PIH, in case of persistent blood pressure ≥140/90 mmHg after 20 weeks of gestation in previously normotensive women, and PE in case of pregnancy-induced hypertension associated with proteinuria ≥300 mg/24 h[10]. FGR was diagnosed when fetal growth was below the 10th percentile for gestational age, using customized growth charts for twin gestations[11]. Gestational hypothyroidism was defined as TSH levels >2.5 mIU/L in the first trimester or >3.0 mIU/L in the second and third trimester[12]. Intrahepatic cholestasis of pregnancy was diagnosed in presence pruritus associated to bile acid levels ≥10 μmol/L[13]. Preterm pre-labor rupture of membranes was defined as pre-labor rupture of membranes before 37 weeks of gestation; PB and very PB were defined as delivery before 37 and 32 weeks of gestation respectively.

No ethics approval was necessary since this analysis used existing records, based on information routinely collected and subjects represent a de-identified data set that was considered exempt from ethical review board.

All data were collected in a computerized database and analyzed by SPSS software (IBM SPSS Statistics 23, IBM Corporation). Women's characteristics were compared in univariate statistical analyses to describe the study population. Pearson's X^2 test and Fisher's exact test were used for the comparison of the qualitative variables, while the Mann-Whitney test was used to compare quantitative data. The results were reported as mean ± SD or percentage as appropriate. $p<0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics of the two groups are described in Table 1. The mean maternal age ± SD were 34.83±3.0 years in Group A and 43.48±2.9 years in Group B. We found a higher incidence of previous miscarriage (17.3% vs 7.5%, p=0,002) and pre-gestational hypertension (6.2% vs 0%, p=<0.001) in Group B than Group A, while no differences in term of BMI and pre-gestational diabetes were found (Table 1).

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Analysing the different type of ART treatment, 97% of women <40 years underwent to autologous FIVET/ICSI comparing to 40% of women ≥40 years underwent to heterologous FIVET/ICSI (p=<0.001), with 6% of embriodonation (Table 1).

Considering pregnancy outcome, a significantly higher incidence of GDM (22.2% vs 13.6%, p=0.021) and PIH/PE (18.5% vs 5.3%, p=<0.001) was showed in Group B than Group A (Table 2).

No statistically significant differences were found regarding the length of pregnancy (p=0.446) and neonatal birthweight (p=0.538) (Table 2).

Evaluating PB, in univariate analysis of twin pregnancies after ART, there was only a trend of higher rate of total PB rate within mother aged ≥40 years old (p=0.104) (Table 2). However, Group A showed higher rate of SPB <37 weeks and <32 weeks (p=0.023 and p=0.002, respectively), whereas Group B showed significantly higher rate of iatrogenic PB <37 weeks of gestation (p=0.001) (Table 2). Nevertheless, maternal and fetal indications for iatrogenic PB <37 weeks and <32 weeks were not significantly different in the two groups (Table 3).

While a higher rate of PB is shown in mother aged <40 years old after autologous IVF/ICSI treatment, a higher incidence of PB was observed in Group B after heterologous treatment (p<0.001) (Table 4). Despite this, the absolute prevalence of PB in the entire population is higher in Group A, both after autologous (22.5%) and heterologous (25%) ART treatment, than in Group B (10.1% vs 21.4%).

Comment

Principal findings

This study first evaluated the association of more than one obstetric risk factor, such as advanced maternal age (≥40 years old,) ART treatment and twin pregnancies.

Analyzing nulliparous women with DCDA twin pregnancies after ART within women <40 years and ≥40 years old, we showed an increased rate of pre-existing disease, such as pre-gestational hypertension and previous miscarriage, as well as gestational diseases, such as PIH/PE and GDM, in women ≥40 years.

Not surprisingly, we found a higher rate of heterologous ART treatment among women ≥40 years old, with a predominant recourse to oocyte donation instead of embryo donation.

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Moreover, we showed that women ≥40 years old have an increased rate of iatrogenic PB <37 weeks of gestation (p<0.001) and, on the contrary, they experienced SPB less frequently at both <37 and <32 weeks of gestation, with a lower prevalence of PB in the case of oocyte donation. The higher incidence of SPB <37 weeks and <32 weeks in women <40 years old in spite of an increased rate of iatrogenic PB in older women should be probably explained by the increased rate of maternal and fetal complications related to the advanced maternal age, even if we did not found a statistically significant difference, in term of indications for iatrogenic PB (Table 3).

Nevertheless, all women should be reassured that the means gestational age at delivery was >34 weeks and mean neonatal birthweight were >2000 grams, independently from maternal age (Table 1).

Our data are coherent with previously published statistics reporting an increased incidence of pre-gestational hypertension and PIH/PE with advanced maternal age[14-17] and the rates of PIH/PE were even higher if ART was used for conception[18].

Similarly, scientific literature demonstrates that advanced-age mothers of are more likely to GDM[19], both older nulliparas and multiparas, suggesting that maternal age, and not parity, might be responsible for the increase in this disease[20], as well as in women undergoing ART[21] and in twinning[22].

Interestingly, our data demonstrated that there are no significantly differences in terms of mean gestational age at delivery and neonatal birthweight. Similarly, only a slight trend toward PB in women ≥40 years old is shown. Scientific data reported on the relation between maternal age, ART procedure and prematurity are still conflicting[4,23] since women who undergo ART are typically older than the general obstetric population and more likely to have multiple births, both factors being important confounders of PB. Coherently to our results, Xiong *et al.* demonstrated that in women undergoing ART the risk of PB decreases with advancing maternal age, both in singletons and twins[24]. Also Martin *et al.* reported that the mean gestational age at delivery was even more favorable in older mothers[25].

We also considered the relation between PB and the autologous or heterologous IVF/ICSI treatment, demonstrating that the prevalence of PB was higher in women <40 years old who underwent the autologous IVF/ICSI and in women aged ≥40 years old who underwent heterologous IVF/ICSI, but with an increased rate of iatrogenic PB. Our results are confirmed by Krieg *et al.* who reported that oocyte recipients

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(maternal age >38 years) were not at increased risk of SPB also in case of multiple gestation, after adjustment for maternal age and multiple gestation[26].

Clinical implications

Many hypotheses focusing on the aging uterus consider it less suited for this challenge than a younger uterus, even if the real impact of uterine aging on pregnancy and neonatal outcome remains to be clearly evaluated. Probably the effect of maternal age on birth outcome in infants conceived with ART may be different from that of infants conceived naturally, and it could be assumed to be an advantage for some conditions, such as PB, in older women who have conceived with ART. The reason for this difference is still not clear; probably the indications of ART treatment with increasing age are different. While reproductive disorders, such as PCOS, endometriosis, and PID, are more frequent in younger women and may affect the reproductive outcome contributing to an increased risk of PTB, with advanced age the most frequent indication is represented by the diminished ovarian reserve.

Whether the ART procedures, anamnestic factors, and maternal age or factors associated with the pre-existing infertility contribute to the adverse pregnancy and perinatal outcomes has been investigated with contradictory results. Infertile women with pre-existing infertility (PCOS, endometriosis, adenomyosis, uterine fibroids, unexplained infertility) could have several alterations in terms of hormonal, inflammatory and metabolic dysfunctions capable of modifying the endometrial, myometrial and placental functions, thus causing poor obstetric outcomes[27], so that infertility itself may increase the risk of adverse obstetrical and perinatal outcomes[9,28,29].

Moreover, it is plausible that additional risks are intrinsic to ART, and the characteristics of women undergoing ART should be considered. On considering oocyte donation, some reports suggested that not only maternal age, but also the allogenic fetus may predispose women to pregnancy modifications[30,31].

All these considerations should be taken into account during the information process to women consulting for twin pregnancy after ART on the basis also of maternal age. Since more women delay childbearing, obstetricians are expected to treat a growing population of older pregnant women. Pre-conception counseling regarding the risks of twin pregnancies after ART with advanced maternal age should be correctly performed and screening for concurrent medical conditions promoted.

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Strength and weakness

Our study has some strengths and limitations. The strengths are mainly represented by the large available dataset and by the study design that first evaluated the association of more than one risk factor in twin pregnancies that were previously evaluated as a single risk factor.

The limitations of our study are first represented by limited number of women who underwent to heterologous ART treatment, since Italian legislation only recently approved this procedure.

Moreover, another limitations is represented by the variable cut-off used in scientific literature to define "advanced maternal age" that may alter the comparison with other studies. In the past, advanced maternal age has frequently been defined as >35 years old at delivery[32], although some authors have used the age limits of 40 years[33] and even 45 years[34]. Since women over the age of 45 who underwent ART and obtained a twin pregnancy are only a minority, we preferred to use the cut-off of 40 years in the belief that due to the effects of increasing age and postponed motherhood, this parameter probably needs to be redefined.

Lastly, a limitation was represented by the absence of the analysis of the postpartum and perinatal outcome. This is related both to the retrospective nature of the study and the difficulty of applying homogeneous obstetric management of twin pregnancies, especially in terms of time of delivery, type of delivery and indications for CD. Since our centers performed elective CD for DCDA twin or vaginal delivery with cephalic presentation of both twins in different ways, we chose to analyze only the maternal and pregnancy outcome, avoiding the evaluation of perinatal outcome in order to eliminate the risk of bias.

Conclusions

Our data indicate that nulliparous twin pregnancies conceived with ART in mothers ≥40 years old did not show significantly higher incidence of PB, even if an increased rate of iatrogenic PB <37 weeks is showed.

Twin pregnancies conceived with ART in women ≥40 years old have a higher risk of obstetrical and perinatal complications than spontaneous pregnancies and although pregnancy disorders such as preterm birth have decreased, constant monitoring should be considered during pregnancy.

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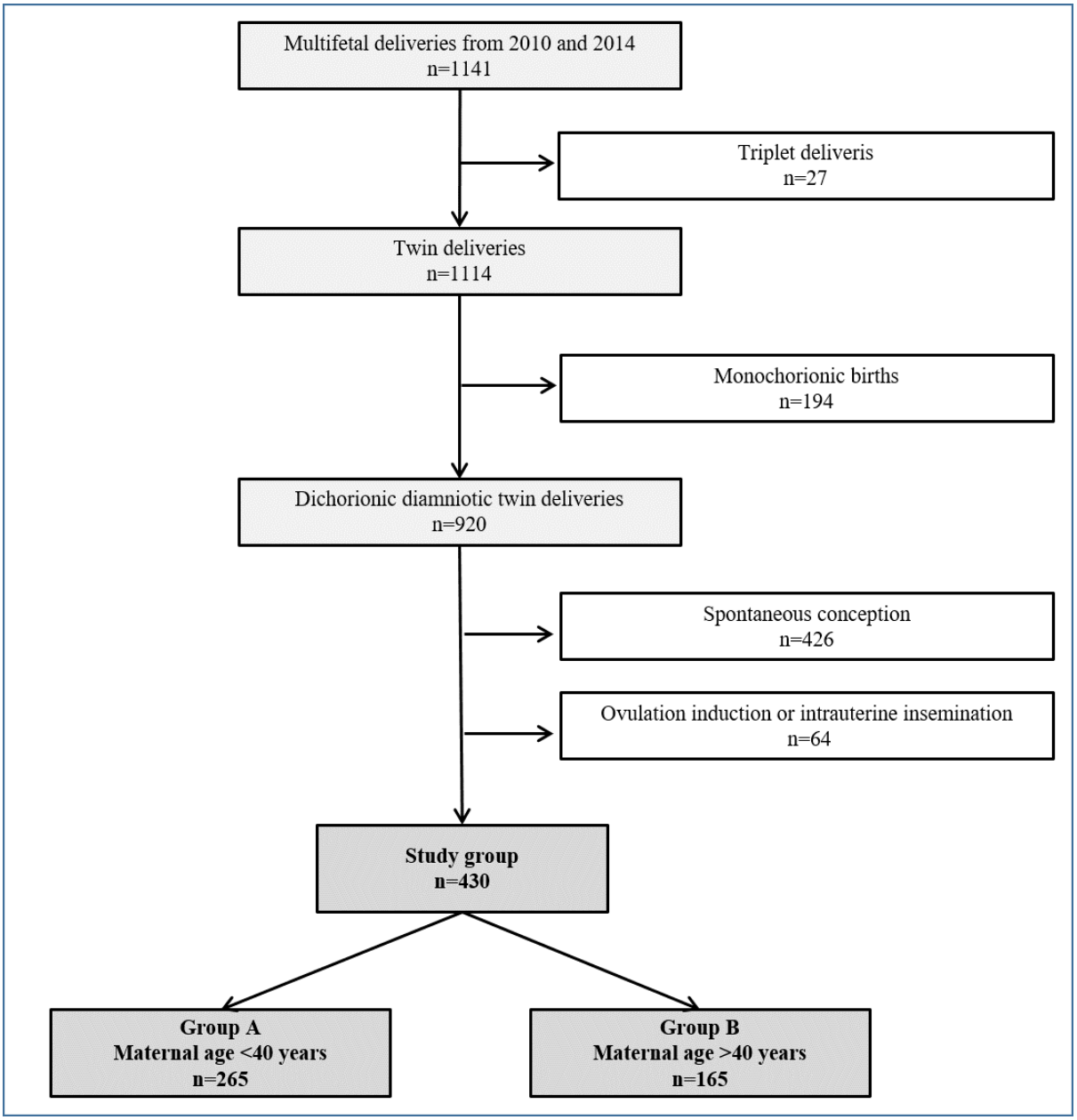
Figures

Figure 1. Flow diagram of inclusion process



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Tables

Table 1. Demographic and clinical characteristics.

	Group A **Age <40 years** **N= 265**	**Group B** **Age 40≥ years** **N=165**	***P* value**	**OR**	**95% CI**
Maternal age (years)	34.83±3.0	43.48±2.9	<0.001†		
Body mass index (kg/m^2)	21.9±2.9	22.76±3.7	0.060†		
Foreign nationality	40 (15.1)	12 (7.4)	0.018*	2.22	1.12-4.37
History of miscarriage	20 (7.5)	28 (17.3)	0.002*	2.56	1.38-4.71
Pre-gestational hypertension	0 (0)	10 (6.2)	<0.001§	36.56	2.12-628
Pre-gestational diabetes mellitus	0 (0)	2 (1.2)	0.143§	8.27	0.39-173
ART treatment					
Autologous IVF/ICSI	257 (97)	99 (60)	<0.001*	21.42	9.92-46.24
Heterologous IVF/ICSI	8 (3)	66 (40)			
Heterologous IVF/ICSI					
Oocyte donation	8 (100)	56 (84.8)	0.587§	3.159	0.17-59.05
Embryo donation	0 (0)	10 (15.2)			

Data are presented as *mean* ± *SD* or *n (%).* SD = standard deviation. OR = odds ratio. CI = confidence interval.
† Mann-Whitney test
* Pearson's X^2 test
§ Fisher's exact test

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Table 2. Pregnancy outcomes.

	Group A **Age <40 years** **N=265**	**Group B** **Age ≥40 years** **N=165**	***P* value**	**OR**	**95% CI**
Gestational hypothyroidism	20 (7.5)	10 (6.2)	0.590*	0.81	0.37-1.76
Gestational diabetes mellitus	36 (13.6)	36 (22.2)	0.021*	1.81	1.09-3.02
Gestational hypertension/preeclampsia	14 (5.3)	30 (18.5)	<0.001*	4.07	2.08-7.95
Fetal growth restriction	50 (18.9)	34 (21)	0.593*	1.14	0.70-1.86
Intrahepatic cholestasis	18 (6.8)	2 (1.2)	0.008§	5.83	1.33-25.4
Preterm pre-labor rupture of membranes	32 (12.1)	28 (17.3)	0.133*	1.52	0.87-2.63
Placenta abruption	12 (4.5)	4 (2.7)	0.306§	1.909	0.60-6.02
Cesarean delivery	253 (95.4)	160 (96.8)	0.600*	0.66	0.23-1.91
Length of pregnancy (weeks)	34.4±3.3	34.6±2.2	0.446†		
Preterm birth	181 (68.3)	124 (75.1)	0.104*	0.69	0.44-1.08
Spontaneous preterm birth					
Spontaneous preterm birth < 37 weeks	60 (22.6)	22 (13.5)	0.023*	1.86	1.09-3.17
Spontaneous preterm birth < 32 weeks	22 (8.3)	2 (1.2)	0.002§	7.24	1.67-31.24
Iatrogenic preterm birth					
Iatrogenic preterm birth < 37 weeks	121 (45.6)	102 (61.8)	0.001*	1.92	1.29-2.86
Iatrogenic preterm birth < 32 weeks	26 (9.8)	12 (7.2)	0.389§	0.72	0.35-1.42
Neonatal birthweight (grams)	2122±597	2131±470	0.538†		

Data are presented as *mean* ± *SD* or *n (%).* SD = standard deviation. OR = odds ratio. CI = confidence interval.
† Mann-Whitney test
* Pearson's X^2 test
§ Fisher's exact test

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Table 3. Indications for iatrogenic preterm birth.

	Group A **Age <40 years** **N=265**	**Group B** **Age ≥40 years** **N=165**	***P* value**	**OR**	**95% CI**
Iatrogenic preterm birth < 37 weeks	121 (45.6)	102 (61.8)			
Fetal indication	85 (70.3)	70 (68.6)	0.068*	1.07	0.61-1.91
Maternal indication	36 (29.7)	32 (31.4)			
Iatrogenic preterm birth < 32 weeks	26 (9.8)	12 (7.2)			
Fetal indication	12 (46.2)	8 (66.7)	0.307§	0.42	0.10-1.78
Maternal indication	14 (53.8)	4 (33.3)			

Data are presented as *n (%)*.OR = odds ratio. CI = confidence interval.
* Pearson's X^2 test
§ Fisher's exact test

Table 4. Preterm birth rate considering ART treatment.

	Group A **Age <40 years** **N=265**	**Group B** **Age ≥40 years** **N=165**	***P* value**	**OR**	**95% CI**
Preterm birth	181 (68.3)	124 (75.1)			
Preterm birth after autologous IVF/ICSI	177 (97.7)	70 (56.4)	<0.001*	34.14	11.91-97.83
Spontaneous preterm birth < 37 weeks	58 (32.7)	10 (14.3)	0.003*	2.92	1.39-6.12
Iatrogenic preterm birth < 37 weeks	119 (67.3)	60 (85.7)			
Spontaneous preterm birth < 32 weeks	22 (37.3)	0 (0)	0.088§	7.8	0.41-145.2
Iatrogenic preterm birth < 32 weeks	37 (62.7)	6 (100)			
Preterm birth after heterologous IVF/ICSI	4 (2.3)	54 (43.6)	<0.001*	34.14	11.91-97.83
Spontaneous preterm birth < 37 weeks	2 (50)	12 (22.2)	0.243§	3.5	0.44-27.54
Iatrogenic preterm birth < 37 weeks	2 (50)	42 (77.8)			
Spontaneous preterm birth < 32 weeks	0 (0)	12	n.c.		
Iatrogenic preterm birth < 32 weeks	0 (0)	8			

Data are presented as *n (%)*.OR = odds ratio. CI = confidence interval.
* Pearson's X^2 test
§ Fisher's exact test