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Original Research

Perinatal outcome in twins. A hospital based comparative study at a single third-level care centre in Croatia

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Background: The goal of our study is to explore the association of assisted reproductive technology (ART) as contributing factor for obstetric complications and perinatal outcome in twin pregnancies during a 14-year period at a single tertiary centre. *Methods*: We collected the data (from maternal and neonatal medical records) from 731 twin pregnancies; 192 conceived by ART and 539 twin pregnancies conceived naturally during a 14-year period. *Results*: Pregnancy complications in twin pregnancies mainly included preterm premature rupture of membranes, gestational diabetes mellitus, and preeclampsia. Higher occurrence of placenta praevia in the ART group was the only perinatal risk related to twin pregnancies in the ART group as compared to those conceived naturally. Over 71% of ART twins were delivered by caesarean section, which is considerably increased as compared to non-ART twins ($P = 0.042$). Neonatal complications in both groups mainly included low Apgar score in the 1st minute, low birth weight and admission to NICU, and the incidences of these complications were comparable between the groups. *Conclusion*: Our results indicated that ART procedures were not followed by adverse obstetric and perinatal outcome in twin pregnancy delivered at single tertiary centre, except for the slightly higher risk of placenta praevia.

Keywords

Twin pregnancy; Assisted reproductive technology; Obstetric complications

1. Introduction

Infertility affects about 13–15% of couples, 30% out of which are diagnosed with idiopathic infertility [1]. The development and worldwide adoption of assisted reproductive technology (ART), mostly in vitro fertilization and embryo transfer (IVF-ET), enabled infertile and subfertile couples to procreate successfully. The wide use of assisted reproductive technology increased the rate of twin birth mostly due to the transfer of two and more embryos [2]. For example, the twin birth rate has increased by 76% from 1980 to 2009 in the United States while in Australia it increased by 15% from 1992 to 2012 [2]. According to latest Centers for Disease Control and Prevention's report, twin births in the United States steadily increased for more than three decades, peaked in 2014 and have fallen 4% since [3]. In Croatia, the twin rate increased by 55% from 1986 to 2018 [4]. As previously mentioned, the incidence of twin birth is higher in the group of ART conceived children with a greater risk for preterm birth and adverse perinatal outcomes as compared to singleton pregnancies [5, 6]. Researches comparing spontaneous conception, and assisted reproductive technology determined that ART pregnancies, unfavourably affect mothers and their new-borns [7, 8]. Although twin pregnancies are known to be associated to a higher risk of maternal and foetal complications as compared to singletons, it is not yet clear whether twin pregnancies following ART are associated with higher risks of obstetric and neonatal complications when compared to naturally conceived twin pregnancies [9, 10]. Conflicting results from some studies [5, 11–13] are derived from the fact that the monochorionic rate among ART-conceived twin pregnancies is quite low, when compared to those conceived naturally, where, according to the Ghalili, more than 20% pregnancies present as a monochorial, which is contrary to most studies [14]. This is important to mention since monochorionic pregnancies present with significantly increased proportion of unfavourable perinatal outcome [15]. It needs to be highlighted that ART pregnancies pose further contributing obstetric risk factors such as advanced maternal age, nulliparity and comorbidity related to infertile couples [16].

Recent literature demonstrates significantly higher rates of preterm birth, increased number of caesarean sections and elevated proportion of small for gestational age in the twins

conceived by ART as compared to those spontaneously conceived [16, 17]. Although high efforts have been put in investigation of the role of ART in maternal and neonatal outcomes of twin pregnancies, many variables remain blurred [5, 11, 18].

The goal of our study is to explore the association of ART as risk factor for obstetric complications and perinatal outcomes in twin pregnancies in 14-year period at single third-level perinatal care centre in Croatia.

2. Materials and methods

The data were retrospectively analysed and included 731 twin pregnancies with > 24 gestational weeks delivered at the Department of Gynaecology and Obstetrics, Clinical Hospital 'Sveti Duh' Zagreb from January 2005 to December 2018. The hospital ethics committee approved the research. The ART group included parents who had undergone in vitro fertilization-embryo transfer (IVF/ET) or frozen-embryo transfer. Twin pregnancies with one vanishing twin and pregnancies with stillbirths were eliminated from the study.

Maternal characteristics included: age, parity, gestational age, pre-existing chronic diseases (thrombophilia, hypothyroidism, hyperthyroidism, heart diseases, chronic hypertension, diabetes mellitus).

Gestational age was calculated using the first day of the last menstrual bleeding. Preterm delivery was determined as delivery at less than 37th gestational week according to the crown-rump length (CRL) measured by ultrasound, in time interval from 11th until 14th gestational week.

Maternal complications related to the current pregnancy included gestational diabetes (plasma glucose level with 75 g oral glucose intake tolerance test; fasting > 5.1, after 60 min > 10.0, after 120 min > 8.5 mmol/L), hypertensive diseases associated with pregnancy: hypertension (blood pressure elevation > 140/90 mmHg after 20 weeks of pregnancy in the absence of proteinuria or other signs of preeclampsia); preeclampsia (hypertension > 140/90 mmHg in association with proteinuria > 0.3 g/24 h urine, or with thrombocytopenia, impaired liver function, liver insufficiency, lung congestion or different cerebral and visual difficulties; HELLP syndrome).

Obstetric outcomes included: preterm premature rupture of membranes (defined as rupture of membranes before the 37th week of gestation), preterm delivery (delivery that occurred before the 34th week of gestation), placenta praevia (defined as after 28 weeks of gestation as the placenta that adhere to the lower portion of the uterus, or lower placental border reaches or covers the cervical orifice or position of placenta is lower than the first exposed foetal body part), placental abruption (determined as after 20 weeks of gestation or during childbirth with normal placental position, but partly or complete torn from uterine wall before foetal delivery), intrauterine foetal demise (verified by an ultrasound examination that documented absence of foetal cardiac activity) and mode of delivery (caesarean section).

Neonatal outcomes included: birth weight, first- and fifth-minute Apgar score < 7, very low birth weight (weight at birth < 1500 g), perinatal death (defined as death between 24th gestational week and the 7th postnatal day), transfer to a NICU, chromosomopathy and malformations (congenital malformations, deformities, and chromosomal abnormalities classified in accordance with the 10th edition of the International Classification of Diseases: Q00–Q99). If growth discordance occurred, then it was determined as a birthweight difference between twins as greater than 25%.

The statistical software package SPSS 26 and RStudio 1.2.1578 were utilised for data analyses. Student's *t*-test (for continuous variables) and the chi-square test (for categorical variables) were applied to determine the association between the various factors under investigation. The Mann-Whitney U test was used for non-continuous variables. The univariate analyses have been performed for being re-used in meta-analyses.

All *P* values of less than 0.05 were perceived as significant.

3. Results

During the analysed time interval, there were 43,100 births in total, out of which 731 (1.69%) were twin pregnancies. Out of all twin pregnancies, 25.58% (n = 192) were ART conceived (Study group).

Maternal age from the Study group was significantly increased as compared to those who spontaneously conceived (Control group) (32 ± 7 vs. 35 ± 8 years, $P < 0.001$). There was no difference in gestational age between the groups (37 ± 3 vs. 37 ± 3, $P = 0.298$). Multiparity in the Control group was significantly higher as compared to the Study group (268 vs. 36, $P < 0.001$).

We have not found differences in gestational age between the groups (37 ± 3 vs. 37 ± 3, $P = 0.298$).

We found no difference in pre-existing diseases between the comparing groups (Table 1).

Pregnancy complications mainly included preterm delivery, preterm premature rupture of the membranes, gestational diabetes mellitus and abruption of placenta, and were comparable between the groups. We found significantly increased proportion of placenta previa in the Study group ($P = 0.005$). A significantly elevated rate of caesarean section was detected in the Study group (71.4% vs. 62.7%) ($P = 0.042$) (Table 2).

Table 3 presents neonatal outcomes. No difference was found in terms of very low birth weight of new-borns between the study groups ($P = 0.242$). Discordance of birth weights and selective foetal growth retardation were also comparable among cohorts. We have not found significant difference in Apgar scores and admission of twins to the neonatal intensive care unit (NICU) between observed groups. No differences were also found in the incidence of chromosomopathies and malformations between the groups. Perinatal mortality in this study consisted of 2 cases of early

Table 1. Maternal characteristics.

	Spontaneously conceived (Control group)	ART conceived (Study group)	*P*
	n = 539	n = 192	
Maternal age, years	32 ± 7	35 ± 8	<0.001
Gestation age, weeks	37 ± 3	37 ± 3	0.298
Parity (≥ 1 birth) (n, %)	261 (48.4)	36 (18.8)	<0.001
Pre-existing diseases (n, %)	7 (1.3)	4 (2.1)	0.492

Table 2. Pregnancy complications.

	Spontaneously conceived (Control group)	ART conceived (Study group)	*P*
	n = 539	n = 192	
Gestational hypertension (n, %)	13 (2.4)	6 (3.1)	0.594
Preeclampsia/HELLP (n, %)	13 (2.4)	9 (4.7)	0.113
Gestational diabetes (n, %)	34 (6.3)	13 (6.8)	0.822
PPROM (n, %)	35 (6.5)	11 (5.7)	0.708
Twin-to-twin transfusion syndrome (n, %)	5 (0.9%)	0 (0.0)	0.333
Placental abruption (n, %)	9 (1.7%)	2 (1.0)	0.737
Placenta previa (n, %)	0 (0.0)	4 (2.1)	0.005
Preterm delivery (< 34 weeks) (n, %)	61 (11.3)	27 (14.1)	0.315
Caesarean section (n, %)	338 (62.7)	137 (71.4)	0.042

PPROM, preterm premature rupture of membranes.

neonatal death related to birth asphyxia and severe respiratory distress syndrome, respectively. There was no documented case of stillbirth in our cohort.

4. Discussion

The increased acceptance and advancements of assisted reproduction methods has led to the increasing success of infertility treatments [19]. Although the incidence of twin pregnancies is increased after IVF-ET treatments, it is still not clarified if they have additional maternal and foetal risks as compared to naturally conceived twin pregnancies. Various studies have been undertaken to explore this problem, but their results are still inconsistent and sometimes even opposite, primarily due to a different types and protocols of obstetric care and delivery management that can influence perinatal outcomes, and potential bias caused by unmeasured confounders. Our intention was to analyse whether ART affect the perinatal outcomes in twin pregnancies as compared to twin pregnancies conceived naturally. The results indicated that ART procedures were not associated to a higher proportion of unfavourable perinatal outcomes in twin pregnancies.

Our reported twin birth rate between groups is consistent and comparable with other published studies [20]. Our results detected higher proportion of women older than 35 in the ART group. In contrast with results from other studies [2, 6, 7], we have not found that ART mothers had higher rate of pre-existing comorbidities as compared to non-ART mothers.

Although we had significantly higher proportion of primiparae in the Study group, the rates of preeclampsia between the groups were comparable. Our results indicated that the rate of very low-birth-weight twins did not differ between the groups as in some reports [2, 7, 21, 22], which can be explained by similar gestational age between the groups showed in our study.

Caesarean section (CS) is a potentially life-saving operation when there are some complications during pregnancy and delivery. In our study, caesarean section rate was significantly higher in the ART group as compared to the Control group (71.4% vs. 62.7%, $P = 0.042$), which is consistent with some of the studies [6, 10, 22]. Some authors have not found significant difference in the CS rate, pointing that institutional differences in management of different conditions are likely to have a role in the variation of results [23, 24]. Major reason for completing the delivery of twin pregnancies by caesarean section at our Clinic is independent of the concept method and lies in the foetal malpositions and malpresentations.

Since 1985 World Health Organization (WHO) suggest optimal rate of CS from 5% to 15% [25], but in the last decade we are witnessing a dramatically high rates of caesarean sections that have become worldwide concern and a major topic for many clinicians. There is increasing trend in the CS rate worldwide [26, 27]. Except main indications for CS, there are many factors influencing the increase in number of CS nowadays, including financial incentives, malpractice liability concerns, differences in the availability and training of clinicians, residents, midwives and nurses, and the rising proportion of private maternity wards where the CS rate is substantially higher [28, 29]. Given this rising problem, WHO warns about potential negative consequences for maternal and infant health [30]. Since 2009 there are slightly but steadily decrease in overall annual caesarean delivery rates of twins in

Table 3. Neonatal outcomes.

	Spontaneously conceived (Control group)	ART conceived (Study group)	*P*
	n = 1078 newborns	n = 384 newborns	
Birth weight (g)	2515 ± 665	2465 ± 616	0.242
Selective IUGR (n, %)	36 (3.3)	8 (2.1)	0.382
Birthweight discordance (n, %)	54 (5.0)	24 (6.3)	0.511
Birthweight (< 1500 g)	84 (7.8)	40 (10.4)	0.262
APGAR 1st min < 7 (n, %)	56 (5.2)	22 (5.7)	0.777
APGAR 5th min < 7 (n, %)	28 (2.6)	12 (3.1)	0.700
Malformations (n, %)	16 (1.5)	2 (0.5)	0.458
Chromosomopathies (n, %)	4 (0.4)	0 (0.0)	0.999
Admission to NICU (n, %)	78 (7.2)	24 (6.3)	0.645
Perinatal death (n, %)	0 (0.0)	2 (0.5)	0.263

NICU, Neonatal Intensive Care Unit.

the US (from 32.9% in 2009 to 31.9% in 2018) [31].

Multiple pregnancy is the greatest avoidable risk of IVF. Pregnancies with twins after ART procedures are related to multiple embryo transfers [32]. It is clear from the experience of some countries that further reduction in the multiple pregnancy rate to single figures is feasible. In his study, Luke concluded that transferring high-quality and one or two embryos is related to reduction of multiple births after ART treatments and ultimately the reduction of the perinatal unfavourable outcomes [33].

Our results showed that twin pregnancies after ART are under increased risk of placenta praevia. This is in agreement with few epidemiological investigations that concluded that ART can increase the incidence of placenta praevia [34]. As we are aware of, only one meta-analysis was undertaken for investigation of the relationship between placenta praevia and ART. Karami *et al.* [34] showed that ART procedures increased the risk for placenta praevia. According to time-trends in risk, in the Nordic countries, the risk for placenta praevia has increased over time in pregnancies after ART procedures as compared to naturally conceived pregnancies [35].

Some studies have reported similar perinatal outcomes for ART and spontaneously conceived twin pregnancies [36, 37], and some found a significant difference [38–42]. Our results illustrated that pregnancies with twins conceived by ART are not associated with significant unfavourable perinatal or obstetric outcomes except for placenta praevia as in Anbazhagan study [10]. It is not clear whether the increased risk for multifetal pregnancies is due to factors related to the reproductive technology procedures or it is associated with maternal factors. One of the possible explanations is transcervical catheter manipulation and uterine contractions due to the prostaglandin release [43]. These unnaturally induced uterine contractions can result with a more frequent embryo implantation in the lower uterine part with increased risk of placenta praevia. Maternal stress, subclinical pelvic inflammatory diseases, previous instrumental and hysteroscopic interventions in the uterine cavity, different micronutrient lack and environmental exposure that are more frequent in subfertile population may contribute to this risk [44]. Some studies demonstrate that the perinatal outcome may vary according to the type of ART treatment (fresh compared to frozen embryo transfer, cleavage compared to blastocyte transfer) [19, 45, 46], but that was not captured in our maternal medical records.

It is still not clear if the elevated risk of unfavourable obstetric outcomes after ART is a direct consequence of the procedures and the technology, or whether it reflects some other factor related to the underlying comorbidity or infertility of the couple. If the problem lies in the ART technology itself, more adverse outcomes would be documented for ART twins [21, 47].

No difference has been found in the group of of very low-birth-weight neonates between the groups ($P = 0.242$). Discordance of birth weights and selective foetal growth retardation were comparable. No significant difference in low Apgar scores and transfer to the neonatal intensive care unit (NICU) has been observed. Some studies found higher rate of low-birth-weight neonates and lower Apgar scores in the ART group [47–49].

The major strength of our study includes the large numbers of twin pregnancies managed and delivered at one single tertiary centre with a standardised protocol of care for all twins. The limitation of our study is the retrospective data collection.

It has been shown that twin pregnancies conceived after ART procedures are associated to a higher rate of caesarean delivery, which is consistent with published recommendations that IVF twin pregnancies may be treated as an independent indication for caesarean section itself [50]. Our study found that the method of conception does not have a negative influence on neonatal outcome. Higher occurrence of placenta praevia in the ART group was the only perinatal risk related to twin pregnancies after ART as to those conceived naturally. The influence of ART on preterm birth is still controversial and needs additional studies.

Abbreviations

ART, assisted reproductive technology; CRL, crown-rump length; CS, caesarean section; IVF-ET, in vitro fertilization and embryo transfer; NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes; WHO, World Health Organization.

Author contributions

DH and VEG conceived the presented idea. DP, TT, ATL, AG and DH were involved in planning and supervising the work. DP and VEG wrote the paper with input from all authors. All authors discussed the results and contributed to the final manuscript.

Ethics approval and consent to participate

This study was approved by the hospital ethics committee (Grant No.: 012-7185/1). All subjects gave their informed consent for inclusion before they participated in the study.

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Conflict of interest

The authors declare no conflict of interest.

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