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### Association of *in-vitro* fertilization twin pregnancy with maternal and perinatal complications

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#### ABSTRACT

**Objective:** To analyze maternal and perinatal complication rates in *in-vitro* fertilization (IVF) twins and spontaneous twin pregnancies. **Methods:** The information on obstetric and perinatal outcomes and complications covering 95 IVF twins and 165 spontaneous twin pregnancies was collected from the medical records of Riga Maternity Hospital. Statistical analysis and adjustment for confounders was performed using the SPSS v24.0 software. The continuous data were compared using the *t*-test and Mann-Whitney *U* test for parametrical and non-parametrical data accordingly. The nominal data were analyzed using Pearson's *Chi*-square test and Fisher's exact test. **Results:** The preterm labor risk, intrauterine growth restriction, fetus weight between IVF and spontaneous twins were not statistically significant ( $P>0.005$ ). At the same time our study revealed a statistically significant association of gestational diabetes and pregnancy induced hypertension with IVF twin pregnancies ( $P=0.025$  and  $P=0.003$ , respectively). Moreover, IVF twins had higher odds to be delivered by cesarean section ( $P=0.001$ ). **Conclusions:** IVF twin pregnancies are associated with a higher risk of development of gestational diabetes and gestational hypertension than spontaneous twin pregnancies.

## 1. Introduction

Infertility affects 10%-15% of couples and is one of the most common causes of disability worldwide[1]. *In vitro* fertilization (IVF) with embryo transfer is one of the most effective and commonly used infertility treatment options[2]. Although European Board & College of Obstetrics and Gynaecology suggests single embryo transfer[3], infertility treatment clinics worldwide including those in Latvia still use double embryo transfer after IVF because of higher birth rate comparing with single embryo transfer. Nevertheless, double embryo transfers are associated with a higher incidence of twinning and higher perinatal complication risk *e.g.* low birth weight and preterm delivery[4].

It is known that pregnancies conceived by IVF also have a higher risk of maternal and perinatal complications, although studies mostly focus on singleton pregnancies and commonly exclude twins from their analysis[5]. Notwithstanding, the data about the safety and complication rates for mothers and fetuses for twin pregnancies conceived by IVF are limited and controversial[6,7].

The aim of our study was to analyze maternal and perinatal complication rates in IVF twins and spontaneous twin (ST) pregnancies.

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## 2. Materials and methods

### 2.1. Study design and patients

To analyze maternal and perinatal complication rate, we completed a retrospective cohort study. The study was approved by the Ethical Committee of Riga Stradiņš University; the protocol number was 26/30.11.2017. The information on the patients perinatal period was obtained from the medical records of Riga Maternity Hospital, the biggest perinatal care center in Latvia. The inclusion criteria were IVF conceived and spontaneously conceived diamniotic twin pregnancies. Mothers with known record of substance abuse were excluded from the study. Maternal complications, obstetric outcomes and twins perinatal complications were analyzed.

### 2.2. Statistical analysis

The statistical analysis was performed using the SPSS statistics v24.0 software. Normal distribution of data was assessed by analyzing histograms and by applying the Kolmogorov-Smirnov test. The continuous data were compared using the *t*-test and Mann-Whitney *U* test for parametrical and non-parametrical data accordingly. The nominal data were analyzed using Pearson's *Chi*-square test and Fisher's exact test. Binominal logistic regression was used to exclude effects of possible confounders *e.g.* maternal age, body mass index (BMI), smoking status, chorionicity as well as parity and mode of delivery, where necessary. Significance level  $\alpha = 0.05$  was used.

## 3. Results

### 3.1. Study group

The study included data about 260 twin pregnancies: 95 (36.5%) were conceived by IVF and 165 (63.5%) were conceived spontaneously. A description of both groups was provided in Table 1. The mean maternal age in IVF group was by 2.1 years higher than in ST group ( $P=0.000$  1). The patients in IVF group also had lower parity ( $P=0.000$  1). The analysis of the systemic diseases showed that patients had only thyroid gland and cardiovascular system disorders of similar frequency between the groups ( $P>0.05$ ). There were no differences in other characteristics between both groups.

### 3.2. Perinatal outcomes

The analyzed perinatal outcomes were similar for both study groups. There were no differences in the weight of twins, frequency of low birth weight infants between IVF and ST groups ( $P>0.05$ ). The frequency of preterm labor was slightly higher in ST group (37.0% *vs.* 30.5%) although the difference was not statistically significant ( $P=0.29$ ).

### 3.3. Maternal outcomes

Analyzing maternal complications, we found that gestational diabetes and gestational hypertension were statistically significantly more common in mothers from IVF twins group,  $P<0.05$  (Table 2). After adjusting for confounders, the association with both

**Table 1**

Description of study groups.

Features	IVF twins group (n=95)	ST group (n=165)	P value
Mean maternal age [(years) (mean±SD)]	33.2±4.0	31.1±5.0	0.000 1
Mean paternal age [(years) (mean±SD)]	35.5±5.0	34.4±7.0	0.150 0
Mean BMI [(kg/m <sup>2</sup> ) (mean±SD)]	29.3±4.0	29.2±4.0	0.860 0
Positive smoking status [n (%)]	3 (3.2%)	10 (6.1%)	0.390 0
Alcohol usage (n)	0	0	NA
Frequency of systemic diseases [n (%)]	10 (10.5%)	13 (7.9%)	0.580 0
Primipara [n (%)]	70 (73.6%)	67 (40.6%)	0.000 1
Median parity (n)	1	2	0.000 1
Monochorionic twins* [n (%)]	2 (2.1%)	34 (20.1%)	0.000 1

IVF: *In-vitro* fertilization; ST: spontaneous twins; NA: not applicable; BMI: body mass index; SD: standard deviation.

\*Only diamniotic twins were included in study.

**Table 2**

Comparison of maternal and obstetric complication frequency between IVF and spontaneous twin groups.

Complications	IVF group (n=95)	ST group (n=165)	P value
Gestational anemia [n (%)]	34 (35.8%)	55 (33.3%)	0.690
Gestational diabetes [n (%)]	11 (11.6%)	7 (4.2%)	0.025
Preeclampsia [n (%)]	12 (12.6%)	17 (10.3%)	0.570
Gestational hypertension [n (%)]	12 (12.6%)	5 (3.0%)	0.003
Urogenital infections during pregnancy [n (%)]	8 (8.4%)	15 (9.1%)	0.860
Uterine dysfunction [n (%)]	6 (6.3%)	14 (8.5%)	0.527
Premature placental abruption [n (%)]	3 (3.2%)	6 (3.6%)	1.000

IVF: *In-vitro* fertilization, ST: spontaneous twins.

complications remained significant. The odds for developing gestational diabetes and gestational hypertension was three times higher [ $P=0.03$ , odds ratio (OR)=3.2, 95% confidence interval (CI) (1.1-9.2)] and six times higher [ $P=0.003$ , OR=6.2, 95% CI(1.9-20.6)] for IVF twins group, respectively. The frequency of other complications did not differ between both study groups (Table 2).

### 3.4. Obstetric outcomes

The most common obstetric complications were uterine dysfunction and premature placental abruption (Table 2). The frequency of obstetric complications did not differ between both study groups ( $P>0.05$ ).

Analyzing modes of delivery (Table 3), we found that IVF conceived twins had statistically significantly higher chances of being delivered via cesarean section [ $P=0.001$ , OR= 2.5, 95% CI (1.1-1.6)], despite the fact that the presentation of twins and the frequency of complications did not differ between both groups. One of the main indications for cesarean section that significantly differed between both groups was “twin pregnancy” (22.1% vs. 4.2%,  $P=0.001$ ). Although after adjustment for confounders, such as maternal age, BMI, parity, chorionicity and smoking status, the association with cesarean section did not remain significant [ $P=0.100$ , OR=1.9, 95% CI (0.9-4.1)].

The postpartum hemorrhage was analyzed separately for three types of delivery (Table 3). The amount of blood loss did not differ between both groups for each mode of delivery ( $P>0.05$ ).

## 4. Discussion

With increasing prevalence of infertility, the application of IVF is rapidly growing[8]. Although IVF is considered as safe procedure, it carries increased risk of certain perinatal and maternal complications. However, there is still an ongoing debate on the risk of different complications, especially in twin pregnancies[9]. Our study demonstrates that IVF pregnancies have a higher risk of gestational diabetes and gestational hypertension. Moreover, twins conceived with IVF have higher odds to be delivered by cesarean section.

In systematic review and meta-analysis, including studies published between 1992 and 2005, McDonald and colleagues[6] have established that IVF twins have increased risk of preterm birth and

low birth weight. We have analyzed several perinatal outcomes *e.g.* low birth weight, lowest weight, as well as frequency of preterm labor. We did not find any increased risk of perinatal adverse outcomes in IVF twins as compared to spontaneously conceived twins. Our study is in line with more recent studies and meta-analysis, which cover a higher number of analyzed pregnancies[7,9,10]. The difference between studies could be explained by improved quality of obstetrical care since 2005 and high difference in complication rate among countries[9].

Only some IVF twin pregnancy safety studies deal not only with perinatal complications[2,6,11], but also with maternal complications. We have established that the risk of gestational diabetes and gestational hypertension is increased in mothers with IVF twin pregnancy. Singleton studies show that IVF pregnancy is associated with the development of gestational hypertension; some of them also reveal increased risk of gestational diabetes, however, the results are conflicting[2,11,12]. There is an ongoing debate in the literature whether the health condition of infertile women [*e.g.* older age, parity, polycystic ovarian syndrome (PCOS)] is associated with increased risk of the development of gestational diabetes and hypertension or those are the side effects of infertility treatment, particularly ovarian stimulation or intake of progesterone during pregnancy[13]. A study that examined the impact of ovulation induction and ovarian stimulation found that pregnancy-induced hypertension is more common in women who had ovulation induction[12]. Also some studies show that IVF singleton pregnancies have higher first-trimester fasting glucose levels[14]. In our study, we have performed adjustments for possible confounders (*e.g.* maternal age, parity, *etc.*), however, we had no access to information on PCOS and other causes of infertility. It is known that infertility is more common for women with PCOS and that PCOS is a risk factor for impaired glucose tolerance, gestational diabetes and hypertension[12,15]. However, studies on women with and without PCOS who underwent IVF and ovarian stimulation reveal that infertility treatment *per se* is associated with increased risk of the described maternal complications[12,16]. Due to the fact that in the majority of countries the screening for gestational diabetes is selective only for high risk groups, it is possible that after IVF women undergo glucose tolerance test more often[12]. This issue, obviously, requires further research for studying the etiology and pathogenesis of increased incidence of gestational diabetes as well as gestational hypertension in IVF group.

Despite the limited extent of data, the available evidence suggests

**Table 3**

Distribution of modes of delivery and amount of blood loss for IVF and spontaneous twin groups.

Groups	Vaginal delivery		Urgent cesarean section		Elective cesarean section	
	Frequency of type of delivery [n (%)]	Blood loss, mL [Median (IQR)]	Frequency of type of delivery [n (%)]	Blood loss, mL [Median (IQR)]	Frequency of type of delivery [n (%)]	Blood loss, mL [Median (IQR)]
IVF group (n=95)	23 (24.2%)	400 (300-500)	46 (48.4%)	700 (575-825)	26 (27.4%)	600 (575-825)
ST group (n=165)	73 (44.2%)	300 (300-400)	58 (35.2%)	600 (500-825)	34 (20.6%)	600 (575-700)

IVF: *In-vitro* fertilization, ST: spontaneous twins, IQR: interquartile range.

that IVF twin pregnancies should be considered a high-risk group for the development of gestational diabetes and the patients should undergo the screening for gestational diabetes.

In agreement with other studies, we found that IVF twins have higher odds to be delivered by cesarean section, however, no statistical significance could be established after adjustment of confounders. The contradictory result can be explained with the fact that in the majority of studies no adjustment for confounding variables was performed, *e.g.* maternal age, smoking status and chorionicity<sup>[17]</sup>. Our study suggests that a higher incidence of cesarean section for IVF twins is the result of confounders rather than an IVF procedure itself.

This study has several limitations, for instance, the study group represents the experience of one facility, and the outcomes might not be generalized. Unfortunately, we do not possess information on the IVF procedure and women or partner infertility causes which can affect the obstetric and perinatal outcomes. Another limitation is that in Latvia the screening for gestational diabetes is selective for risk groups only and to improve the study design—oral glucose tolerance tests should be performed also before pregnancy and for all study participants. However, arterial pressure measurements were performed for each pregnant female at certain time intervals.

### Conflict of interest statement

The authors declare no conflict of interest.

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