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Outcomes of pregnancy and delivery following in vitro fertilization

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Abstract. *Background:* Researchers discuss the influence of *in vitro* fertilization (IVF) on outcomes of pregnancy and delivery. The aim of the study was to evaluate the most frequent complications after IVF. *Materials and methods:* A retrospective analysis was conducted at LSMU Kaunas Clinics. The sample consisted of 69 IVF pregnant women registered in LSMU Kaunas Clinics in 2019-2020. The results were compared to the control group (n=174). Differences were considered significant when $p < 0.05$. *Results:* The frequency of miscarriage after IVF was 14.5% (4.6% in the control group) ($p < 0.05$). Preterm labor was detected in 20.3% of IVF subjects (14.9% in the control group) ($p > 0.05$). Higher rates of preeclampsia, gestational anaemia and obstetric cholestasis were found in the IVF group (7.2%, 8.7%, 5.8%) (2.9%, 6.9%, 0.57% in the control group) ($p > 0.05$). A difference was found in both Apgar scores – 1st and 5th minute. IVF newborn average scores were 8.77 and 9.33, respectively (8.96 and 9.58 in the control group, respectively). 52.2% of IVF subjects had Caesarean section (CS) (26.4% in the control group) ($p < 0.05$). 75.8% of CSs in the study group were performed on multiparous pregnancies (14.3% in the control group) ($p < 0.05$). *Conclusions:* Our study revealed an increased risk of miscarriage and premature delivery after IVF. IVF pregnant women are more likely to be diagnosed with preeclampsia, gestational anaemia and obstetric cholestasis. There is a higher probability to have a CS after IVF compared to natural conception. IVF newborns are rated with lower Apgar scores in comparison to those conceived naturally.

Keywords: IVF, pregnancy, delivery, outcomes.

Introduction

In vitro fertilization (IVF) is often used to overcome the constantly increasing problem of infertility. 471 men and 4341 women were diagnosed with infertility in 2019 in Lithuania [1]. Fertility disorders are detected in 20-30% of men, 20-35% of women and in 25-40% of both. However, reproductive medicine is evolving rapidly and addressing increasingly complex infertility problems [2]: one million newborns were born by IVF in the United States alone between 1987 and 2015 [3]. Additionally, IVF is also used to prevent the inheritance of lethal diseases, to reduce the transmission of HIV and to assist those undergoing cancer treatment [2]. According to global data, the rate of successful IVF is 2 - 29% depending on age (the frequency of success decreases exponentially in older patients) [4]. Only 23.1% of pregnancies initiated by IVF are reported to be non-complicated [4]. The most frequent complications of pregnancy include miscarriage, preterm birth [5], gestational diabetes and gestational hypertension [6]. The most common outcome during delivery after IVF is a caesarean section (CS) [7]. The link between outcomes and causes of infertility, comorbidities, and older parental age has been confirmed [8]. IVF often results in multiple pregnancies, which are associated with preterm birth and low birth weight, leading to developmental disorders and higher mortality rates among newborns. Gonadotropins are also used during infertility treatment: suprafysiological estradiol levels can cause hypertensive pregnancy disorders and lead to fetal growth complications [9]. Our study analyses complications and outcomes of pregnancies and deliveries of women after IVF who gave birth in Lithuanian University of

Health Sciences (LSMU) Kaunas Clinics during 2019-2020 period.

Materials and methods

Study Population

A retrospective study was designed to review the outcomes of women who underwent *in vitro* fertilization at the Clinic of Obstetrics and Gynecology of LSMU Kaunas Clinics. Depersonalized data from the hospital database have been received in March 2021. During the hospitalization every patient has signed an informed consent, allowing the usage of depersonalized data for retrospective studies.

Data Collection

The required sample size was calculated using "Sample Size Calculation for X-Sectional Surveys". The sample consisted of 69 IVF pregnant women who gave birth in LSMU Kaunas Clinics in 2019-2020. The obtained results were compared to the control group (n = 174). The control group was selected randomly from all women who gave birth in the same clinic, excluding pregnancies initiated by other assisted reproduction techniques in order to obtain accurate results. The study was authorized by the Ethics Committee of the Lithuanian University of Health Sciences.

Statistical Analysis

Statistical analysis was performed with IBM SPSS 22.0 software. Categorical variables were presented in per cent and were analyzed with chi-square statistics. Significant differences were considered when $p < 0.05$.

Results

The youngest woman in the IVF subject group was 27 years old, the oldest - 49 years old, and in the control group 25 and 45 years, respectively. The mean age of IVF subjects was 34 years compared to 31 in the control group. The results demonstrate that IVF is more frequently chosen by older women.

Pregnancy outcomes after in vitro fertilization

Miscarriage was observed statistically significantly ($p < 0.05$) more often in women fertilized by IVF compared to women who conceived naturally: spontaneous abortion rates

were 14.5% in the study group and 4.6% in the control group. Among all pregnancies initiated by IVF, 20.3% ended with preterm labor (14.9% in the control group) ($p > 0.05$) (Table 1). The same frequency of gestational hypertension (5%) was detected in both groups. It was estimated that anemia occurred more frequently in women after IVF than in women who became pregnant naturally ($p > 0.05$). One of the most common complications was gestational diabetes, which was found in a quarter (25%) of pregnant women in both groups. The incidence of cholestasis in pregnant women after IVF was 5.8% compared to 0.57% in the control group. The prevalence of preeclampsia was also assessed: 7.2% in the IVF group and 2.9% in the control group ($p > 0.05$).

Table 1. Fetal Outcomes and Apgar Evaluation Comparison

	Multiple pregnancies, (%)	Fetal hypotrophy, (%)	Preterm delivery, (%)	Apgar score	
				1 min.	5min.
Study group (n=69)	47.8*	10.1	20.3	8.77	9.33
Control group (n=174)	4	5.2	14.9	8.96	9.58

* $p < 0.05$ when comparing study group with a control group

More than one-tenth (11.6%) of IVF pregnant women had gynecological diseases (4.97% - endometriosis, 4.97% - fibroids, 1.66% - vaginal cyst). The incidence of thyroid disorders in IVF pregnant women was found to be 26% (13% hyperthyroidism and 13% hypothyroidism).

The frequency of multiple pregnancies differs statistically significantly between the study and control groups: 47.8% in IVF pregnant women and 4% in naturally pregnant women ($p < 0.05$). Fetal hypotrophy was observed in 21.3% of

multiple pregnancies in the study group (5.2% of one twin and 6.1% of both twins). Overall, the incidence of fetal hypotrophy was 10.1% in the IVF group (including both multiple and singleton pregnancies), which was higher 5.2% than in the control group ($p > 0.05$) (Table 1).

Neonatal outcome evaluation was limited to Apgar scores. A difference was found in both scores – 1st and 5th minute. In the IVF group the average 1st minute score was 8.77 and 5th minute score was 9.33. In the control group scores were

slightly higher: 1st minute score was 8.96 and 5th minute score was 9.58 (Table 1).

Delivery outcomes after in vitro fertilization

Deilvery outcomes in the study and control groups were calculated using the same sample, excluding pregnancies that ended in miscarriage. 52.2% of IVF pregnant women had Caesarean section (CS), while in the control group 26.4% deliveries were completed using the same surgery ($p<0.05$) (Table 2). It was detected that 75.8% of CSs in the study group were performed

in multiparous pregnancies ($p<0.05$) and 14.3% of CSs in the control group ($p>0.05$) (Table 2). For one-fifth (20%) of subjects in the IVF group CS was performed due to non-progressive labor activity, 14.5% - due to breech presentation and 7.2% - due to transverse presentation (Table 2). Less common indications that led to CS were placenta previa, clinically narrow pelvis, and umbilical cord complications. *Atonia uteri* was present in 5.8% of cases in the study group. The results of most common indications of CS in IVF group were not compared to the control group.

Table 2. Frequency and most common indications of cesarean section

	Frequency of cesarean section		Frequency of caesarean section in multiparous pregnancies		Cesarean section due to non-progressive labor activity	Cesarean section due to breech presentation	Cesarean section due to transverse presentation
	%	p	%	p	%	%	%
Study group (n=59)	52.2	$p<0.05$	75.8	$p<0.05$	20	14.5	7.5
Control group (n=166)	26.4	$p<0.05$	14.3	$p>0.05$	N/A	N/A	N/A

Discussion

Perceptions of Infertility and IVF

According to our study results, IVF is more frequently performed on women who are older and have more comorbidities. We established that some of IVF pregnant women had preexisting thyroid diseases and gynecological conditions (e.g. endometriosis and myoma), which may be contributing factors of infertility.

Endometriosis is known to affect fertility and occurs in 6 to 10% of the general female population [10]. Furthermore, about 25 to 50% of infertile women have endometriosis [11]. Our research findings have showed that 4.97% IVF subjects were diagnosed with endometriosis and only 0.57% in non-IVF group had the same comorbidity. One study also reports the association of uterine miomas with infertility in

2–3% of analysed cases [12]. Regarding to our study, 4,97% of IVF group subjects were diagnosed with this condition that may lead to IVF. Thyroid dysfunction has also been linked to reduced fertility and increased rates of adverse outcomes such as premature delivery or low birth weight: retrospective and prospective studies claim that 5.8% and 2.1% of women with hyperthyroidism have primary and secondary infertility, respectively [13]. One study investigated 122 patients who underwent IVF unsuccessfully: 70% had at least one abnormal immunological test (including thyroid autoantibodies), compared with only 10% in fertile controls [14]. The incidence of thyroid disorders in our study was 26%. However, the frequency of thyroid disorders in the IVF group was not compared to the control group.

Pregnancy outcomes after IVF

Our research data demonstrated the link between spontaneous miscarriage and IVF, which has also been confirmed in other studies. Researchers attribute the increase of miscarriages to older-aged women who tend to become pregnant with assistance of IVF and to the increasing risk of chromosomal abnormalities with age [15]. However, recent findings report that IVF itself does not increase the preponderance for any specific type of cytogenetic abnormality in patients aged over 35 years [16]. Other significant contributing factors to pregnancy loss are considered to be a number of previous miscarriages and endometrial thickness on the day of embryo transfer [15]. Preterm delivery is also commonly associated with IVF. Higher rate of preterm delivery was detected in all three groups with IVF (<32 weeks, 32-36 weeks, <37 weeks) compared to the control group in a recent

research [17] and the results are similar to those of our trial. The increased risk of preterm delivery after IVF is mostly associated with multiple pregnancies and iatrogenic complications, including hormonal disbalance [18]. Previous trials have showed that IVF pregnancies are linked to higher risk of hypertensive disorders such as gestational hypertension, preeclampsia and eclampsia [19]. However, our findings of gestational hypertension did not differ between IVF and non-IVF groups. We have to note that in our study women in the control group were selected randomly from those who gave birth in Kaunas clinics and often are at higher risk of pregnancy complications such as gestational diabetes, obesity *etc.* Fetal hypotrophy is not a commonly explored feature of similar studies. It is currently established that this complication is either a consequence of the IVF procedures or inherent to the infertility problems *per se* [20]. However, our findings confirm that the frequency of fetal hypotrophy in IVF pregnant women is higher than in women who conceived naturally. More findings related to this topic need to be reported for further discussion.

Delivery outcomes after IVF

Our results have showed particularly high frequency of CS in the IVF group – 52.2% and a number of scientific trials report similar data [7, 9]. One of the researches has shown that rates for CS appear to be disproportionately high in term singleton births after IVF and CS is in some cases performed without any indications [9]. Therefore, vaginal birth should be encouraged and the CS should be chosen based on the conditions of each separate case. Another research has revealed 69% frequency of CS in

IVF group compared to 44% in non-IVF group. The authors report the same problem that many CSs are performed with no necessity of CS, indicating IVF as a main reason [17]. However, recent findings confirm that no higher risk by vaginal delivery was detected compared to CS [5]. Many CSs in our studies were made due to indications such as multiparous delivery, breech presentation, placenta previa etc. Nonetheless, there is a minority of cases in our IVF group that does not declare any specific indication why CS had to be performed.

Conclusions

Our study revealed an increased risk of miscarriage and premature delivery after IVF. IVF pregnant women are more likely to be diagnosed with preeclampsia, gestational anaemia, obstetric cholestasis. There is a higher probability to have a CS after IVF compared to natural conception. IVF newborns are rated with lower Apgar scores in comparison to those conceived naturally.

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Conflict of interest

The authors declare no conflict of interest.

Publication ethics

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Bioethics Centre, Lithuanian University of Health Sciences (Protocol number BEC-MF-194) on 2021 February 5th.

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