Original article

Early Vital Indicators of Newborns Born After Medically Assisted Reproduction

Ana-Maria Milas [*1], Silvija Pušeljić [2,3], Jerko Arambašić [4], Matej Šapina [2,5], Višnja Tomac [2,5]

1 Institute of Maxillofacial and Oral Surgery, University Hospital Centre Osijek, Croatia
2 Department of Paediatric Neurology, Genetics, Endocrinology and Metabolic Diseases, Paediatric Clinic, University Hospital Centre Osijek, Croatia
3 Josip Juraj Strossmayer University of Osijek, Faculty of Medicine Osijek, Croatia
4 Institute of Cardiology, University Hospital Centre Osijek, Croatia
5 Paediatric Clinic, University Hospital Centre Osijek, Croatia

*Corresponding author: Ana-Maria Milas, milas.anam@gmail.com

Abstract

Aim: In this case-control study we wanted to compare the perinatal outcome of naturally conceived newborns to those born after in vitro fertilization (IVF).

Methods: At the University Hospital Centre Osijek, in the period from January 2014 to December 2016, we analysed 120 in vitro fertilization pregnancies and compared to 120 natural conception pregnancies. Characteristics of mothers, birth method, perinatal outcome, and vital characteristics of newborns were analysed.

Results: IVF-ET pregnancies included 70.0% singleton pregnancies, 28.3% twin and 1.7% triplet pregnancies, while all naturally conceived pregnancies were singletons. When pregnancies were compared between IVF-ET and naturally conceived groups, the following characteristics of mothers were established: age 34.83 (5.8):30.39 (3.9); previous pregnancy 13.3%:56.7%; complications in pregnancy 50.0%:25.0%; Caesarean section (CS) 69.2%:35.8%. All of these were statistically significant ($p < 0.001$). Comparison of newborns between those two groups established the following: prematurity 39.5% vs. 12.7%; lowest BW 2,114 vs. 3,000 grams; lowest GA 22.29 vs. 28.71 weeks. In the IVF-ET group, 5.7% of newborns had a gestational age of 22-25 weeks, but there were no newborns of that gestational age among the naturally conceived newborns. These were also statistically significant differences ($p < 0.001$). Apgar score was 10 for both groups, but the difference was in the interquartile range, the values of which were lower in the IVF-ET group.

Conclusion: In vitro fertilization pregnancies are high risk due to the characteristics of both the mother and the infant and, as such, require special attention and care.

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Introduction

The first baby girl born through medically assisted fertilization (MAF) was born back in 1978, and nowadays children that have been born through implementation of this technique make up 1.7% to 4.0% of the population in developed countries [1, 2]. There are only a few fields in medicine that have progressed as rapidly as MAF, which, today, represents the last resort for infertile couples. Clinical guidelines indicate that the availability of a high-quality in vitro fertilization (IVF) and embryo transfer (ET) programme can significantly contribute to the birth rate [3]. After four decades of experience in the field of MAF, there are now relevant studies being conducted in China, Australia, Great Britain and Belgium, which clearly show that children born after MAF differ from naturally conceived children [4-7] in terms of perinatal outcome and vital characteristics. Although available studies differ in methodology, they all include a comparison of pregnancies conceived after MAF (number of foetuses, complications in pregnancy) and of perinatal outcomes (gestational age, birth weight) after naturally conceived pregnancies [4-11]. Those studies have shown that newborns born after IVF-ET are more sensitive during the perinatal period in comparison to newborns born after naturally conceived pregnancies. Such results are to be expected because the characteristics of women who undergo MAF differ from those of women from the general population (higher age, lower parity, comorbidity, infertility or subfertility). It has been demonstrated that MAF methods have contributed to a greater number of multiple pregnancies, primarily twin pregnancies, but also triplet and quadruplet pregnancies [13].

Studies conducted in Croatia are consistent with the results of the above-mentioned research, and they likewise show that there are significantly more multiple pregnancies in the IVF group than with naturally conceived pregnancies [8, 14]. Newborns from the IVF group are born with lower birth weight (BW) and gestational age (GA), and they stay in the intensive care unit (ICU) longer after birth. By researching available literature, we observed that there is a 30-40% higher risk of congenital malformations after the IVF-ET procedure, and this population had a higher incidence of perinatal mortality [5, 8, 10].

Perinatal outcomes of newborns born after MAF also vary in regard to the different methods of MAF. A pilot study conducted in Vienna from 2003 to 2009 in a tertiary health care centre showed a poorer perinatal outcome (lower BW, lower GA, lower Apgar score) among children who were conceived using the ICSI method, compared to children who were conceived after IVF-ET treatment [15].

The association of IVF with neurodevelopmental disorders has been demonstrated in numerous published studies, which showed that children born after IVF have an increased risk of developing cerebral palsy, as well as various disorders resulting from erroneous genomic imprinting [4, 5, 16]. In exploring the relationship between IVF and autism spectrum disorders (ASD), we found conflicting studies. A Swedish study, which was conducted over a period of 25 years, showed that the IVF procedure was not associated with a higher risk of ASD, but with a significantly higher risk of developing mental retardation. On the other hand, meta-analysis by Liu et al. showed that MAF was associated with a higher percentage of ASD [17, 18].

In accordance with these findings, it is justified to claim that the perinatal outcome of IVF cannot be equal to the outcome after natural conception, bearing in mind the diseases and conditions which led to the need for assisted fertilization; likewise, pregnancies after MAF are high-risk pregnancies, whether they are singleton or multiple. The aim of the study was thus to examine the difference in the vital characteristics of newborns born after medically assisted fertilization in comparison with natural conception, as well as characteristics and the course of pregnancy in women who conceived through medically assisted fertilization and those who conceived naturally.

Material and Methods

The study was designed as a three-year retrospective case-control study and was conducted in the Gynaecology Clinic and neonatal intensive care unit (NICU) of the University Hospital Centre Osijek. The study included all infants who were born from pregnancies through assisted reproduction and the first following infant born after natural conception at the University Hospital Centre Osijek from 1 January 2014 to 31 December 2016. Ethical approval for this study was given by the Ethics Committee of the Faculty of Medicine.

General data on the mother (age, occupation, marital status), parity data (number of births, number of miscarriages, accompanying comorbidities, pregnancy and comorbidities during pregnancy) and data on the characteristics of newborns (sex, length, Apgar score) were collected.

Statistical analysis

The data were analysed using statistical procedures for testing differences and correlations, using the statistical program SPSS 17.0. The mean values of the continuous variables are expressed by the arithmetic mean and standard deviation for normally distributed variables and the median and interquartile range for variables that are not normally distributed. The Mann-Whitney U test for nonparametric analysis was used to determine the differences between the two independent samples. The $\chi 2$ test was used to determine the differences between the proportions between the two independent samples. Statistical significance was accepted for $p < 0.05$.

Results

A total of 240 births were analysed, of which 120 were pregnancies after IVF-ET, while the control group included pregnancies where birth occurred immediately after the observed IVF birth, likewise a total of 120 births. Since there were multidisciplinary pregnancies among the observed pregnancies, a total of 277 subjects were included in the study.

A total of 240 mothers was divided into two groups – the control group, or 120 mothers that conceived naturally, and the IVF group, or 120 mothers that conceived after IVF-ET treatment. Mothers in the IVF group are older than those in the control group (arithmetic mean ((SD) of age 34.83 (5.8) vs. 30.39 (3.9)), $p < 0.001$. According to the level of education, mothers from the IVF group have a higher level of education (academic degree), while mothers from the control group predominantly have a low or medium level of education (secondary school degree, primary school or no education), which is a statistically significant difference, $p < 0.001$ (Figure 1).

Figure 1. Level of education of mothers

		Control group n = 120 (%)	IVF group n = 120 (%)	p* (χ^2 test)
Level of education	High or higher (academic degree)	29 (24.2)	66 (55.0)	< 0.001
	Low or medium (secondary school, primary school, no education)	91 (75.8)	54 (45.0)	

Figure 2. Previous pregnancies and miscarriages by groups

		IVF n = 120 (%)	Control group n = 120 (%)	p* (χ2 test)
Pregnancies	**Yes**	16 (13.3)	68 (56.7)	< 0.001
	No	104 (86.7)	52 (43.3)	
Miscarriages	No	95 (79.2)	96 (80.0)	> 0.999
	Yes	25 (20.8)	24 (20.0)	

A significantly higher portion of mothers in the IVF group had not been pregnant before ($p < 0.001$; $^{*}\chi 2$ test), as shown in Figure 2. Comparison of the previous number of miscarriages by group did not show a statistically significant difference between the groups, $\chi 2$ test ($p > 0.999$) (Figure 2).

Of the total number of mothers (240), 150 (62.5%) mothers experienced no complications during pregnancy (HELLP syndrome, bleeding, use of tocolytics, etc.). However, group distribution shows that more complications during pregnancy were experienced in the IVF group (60% of mothers with complications are from the IVF group).

Statistically significant differences were found for the groups in regard to the method of delivery, $\chi 2$ test ($p < 0.001$). Vaginal delivery was the predominant way of giving birth within the control group, whereas pregnancies within the IVF group were mostly completed by Caesarean section, as shown in Figure 3. The highest portion of pregnancies in this study were singleton pregnancies, followed by twin pregnancies. Triplets were found in two pregnancies. All multiple pregnancies were from the IVF group, as shown in Figure 4.

Figure 3. Method of delivery

	IVF group n = 120 (%)	Control group n = 120 (%)	p* (χ^2 test)
Vaginal	37 (30.8%)	77 (64.2%)	< 0.001
CS	83 (69.2%)	43 (35.8%)	

Figure 4. Distribution by number of offspring between groups

	IVF group n = 120	Control group n = 120	p* (χ^2 test)
Singletons	84 (70.0%)	120 (100%)	< 0.001
Twins	34 (28.3%)	0 (0.0%)	
Triplets	2 (1.7%)	0 (0.0%)	

When comparing these two groups based on the sex of the newborn, there were no statistically significant differences. Statistically significant differences were found for every numerical variable (birth weight, gestational age, Apgar score) except for the mean value of pH (p = 0.747). Mean gestational age in the IVF group was 35.57 weeks (22.29 – 37.57), and it was 38.14 (28.71 – 39.29) weeks in the control group. The shortest duration of pregnancy in the control group was 28.71 weeks, and it was 22.29 weeks in the IVF group (Figure 5). The distribution of newborns by gestational age within the groups shpwed that two children were born between the 22nd and 25th week of pregnancy in the IVF group (p < 0.001; Fisher's exact test), while there were no births within that period in the control group (Figure 6).

Figure 5. Duration of pregnancy (in weeks)

	Number of mothers	Arithmetic mean (SD)	Minimum	Maximum
Control group	120	38.92 (2.06)	28.71	42.14
IVF group	120	36.22 (4.39)	22.29	40.86

(data are shown as arithmetic mean and standard deviation (SD))

Figure 6. Distribution of newborns by gestational age

Gestational age (weeks)	IVF group Number (%)	Control group Number (%)
22-25	9 (5.7)	0 (0.0)
26-29	10 (6.4)	1 (0.8)
30-33	12 (7.6)	3 (2.5)
34-36	31 (19.7)	10 (8.4)
37+	95 (60.5)	105 (88.2)

There were 12% of births in control group which were premature (N =12), while 39% of total births in IVF group were preterm births (N = 62). The high proportion of multiple pregnancies within the IVF group resulted in a significantly higher percentage of prematurity in that group, (p < 0.001; $\chi 2$ test, ǂMann-Whitney U test, data not shown). Likewise, the birth weight of the newborns in the IVF group was lower than of those in the control group, as was expected. The lowest birth weight in the IVF group was 2114 grams, and the highest was 3330 grams. In the control group, the lowest birth weight was 3000 grams, and the highest 3785 grams; these values were significantly different between the groups. In spite of the same median of the average Apgar score, which equals 10 in both groups, the difference is in the interquartile range, which is shifted to lower values (9.5-10) in the IVF group (data not shown).

Figure 7. Birth weight distribution of newborns

	Median (25.00-75.00)	
	IVF group (range)	**Control group (range)**
Birth weight (grams)	2880 (2114 - 3330)	3350 (3000 - 3785)

Discussion

Research regarding the vital characteristics of newborns born after in vitro fertilization has not been conducted so far at the University Hospital Centre Osijek, even though medically assisted fertilization has been performed in this institution in accordance with the highest standards for over a decade.

Since our search of the literature did not produce any studies that compare the socioeconomic characteristics of the mother, such as the mother's level of education and marital status, we included these parameters in our study. The results were as expected: there is a significantly higher percentage (55.0%) of mothers with a high or higher level of education in the IVF group, while in the control group this percentage is 24.20%. Such a result can be explained by an increase in the number of women in the academic community, their commitment to their careers and professional development and, consequently, the postponed maternity. This result can also be directly related to the mothers' age – the average age of IVF mothers was 34.88, while it was 30.39 in the control group. This result is consistent with the result obtained in a study that included the same parameter, but which also linked singleton pregnancy with higher maternal age, which was not analysed in our study [19]. By observing the mothers' marital status, we found that there is a higher percentage of mothers who are married that conceived by IVF, compared to the control group. This result did not surprise us, given that the goal of most married couples is to have children, which means that they have to treat infertility if it exists. In the IVF group, 110 (91.70%) mothers were married, while 97 (80.80%) mothers were married in the control group.

As expected, the IVF group contains 104 (86.7%) mothers that had not been pregnant previously, which is statistically significant when compared to the control group, where the observed pregnancy was the first pregnancy for 52 (43.30%) mothers. This brings us back to the definition of medically assisted reproduction, which states that this method is the last resort for treating infertility [3]. Even though we could assume that mothers from the IVF group have a higher incidence of miscarriages, there is no statistically significant difference in this parameter between the two groups.

Out of a total of 240 respondents, 150 of them (62.50%) experienced no complications during pregnancy, but when analysed each group individually, 60 (50.0%) of the IVF mothers experienced complications during pregnancy, while that number was 30 (25.0%) in the control group. This result is not surprising, since the mothers who conceived through IVF could not conceive naturally, which is also why they have a more complicated pregnancy.

Out of the total number of pregnancies (240), 126 (52.50%) were finished with the Caesarean section. If we divide that number according to group, we get a statistically significant difference ($p < 0.001$). 69.2% of Caesarean sections were performed in the IVF group, while vaginal birth occurred in 30.80% of women. In contrast, in the control group, 35.80% of pregnancies were completed with the Caesarean section and 64.20% of women experienced vaginal birth. The obtained number can be directly related to the number of newborns, where we also found a statistically

significant difference ($p < 0.001$). Out of 120 pregnancies in each group, 28.30% of them in the IVF group were twin pregnancies, while 1.70% of them were triplet pregnancies. In the control group, all pregnancies were singleton pregnancies. The fact that all multiple pregnancies were in the IVF group justifies the prevalence of Caesarean section as the method of delivery, since multiple pregnancy is one of the indications for Caesarean section. Our results from this study are similar to those obtained in studies that also compared these parameters [8, 19]. Taking into account the data from the previous section, shorter duration of pregnancies in the IVF group in comparison with the control group is justified. The shortest pregnancy in the IVF group lasted 22.29 weeks, while the shortest one in the control group lasted 28.71 weeks. If we put those numbers in the context of perinatal outcomes, we get a statistically significant difference for a newborn child. There is a higher incidence of premature infants in the IVF group than in the general population. When duration of pregnancies was expressed in weeks and analysed both groups, one could observe that there are no newborns born between the 22nd and 25th week in the control group, and only one newborn born between the 26th and 29th week. Most children are born "at full term", i.e. 88.20% from the 37th week onwards. In the IVF group, the situation is very different. 5.70% (9) of the newborns were born in the critical period between 22 and 25 weeks, and "only" 60.50% from the 37th week onwards. It is clear that all of the above parameters also affect the birth characteristics of newborns in both groups. Median birth weight in the control group was 3,350 grams, with a higher lowest birth weight than the one in the IVF group. In the IVF group, median birth weight was 2,880 grams, with the very low 2,114 grams as the lowest value. The highest birth weight in the IVF group was lower than the average birth weight in the control group, which is not significantly different from data in other studies [8, 19, 20].

Conclusion

With the direct link between medically assisted reproduction and low birth weight, as with gestational age in this study and high maternal age, we can conclude that IVF-conceived pregnancies are high-risk pregnancies and should as such receive special attention and care. Since medically assisted reproduction is more common now than it was before, it is the right time to see early vital indicators and collect them to compare with later data. This study thus opens a lot of possibilities and indicates the need for long-term prospective follow-up of these respondents, in order to obtain more information and findings about the outcomes of children born after medically assisted fertilization.

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[i] **Author contribution.** Acquisition of data: Milas AM, Pušeljić S, Arambašić J, Tomac V
Administrative, technical or logistic support: Milas AM, Pušeljić S, Arambašić J, Tomac V
Analysis and interpretation of data: Milas AM, Pušeljić S, Arambašić J, Šapina M, Tomac V
Conception and design: Milas AM, Pušeljić S, Arambašić J, Šapina M, Tomac V
Critical revision of the article for important intellectual content: Milas AM, Pušeljić S, Arambašić J, Šapina M, Tomac V
Drafting of the article
Final approval of the article

Guarantor of the study: Milas AM, Pušeljić S, Arambašić J, Šapina M, Tomac V
Obtaining funding: Milas AM, Pušeljić S, Arambašić J, Šapina M, Tomac V
Provision of study materials or patients: Milas AM, Pušeljić S, Arambašić J, Tomac V
Statistical expertise: Milas AM, Pušeljić S, Arambašić J, Šapina M, Tomac V
Other: Milas AM, Pušeljić S, Arambašić J, Šapina M, Tomac V