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ORIGINAL ARTICLE

Pregnancy outcome after in vitro fertilization: a retrospective cohort study

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ABSTRACT

Aim To determine the outcome of pregnancies in women whose pregnancies resulted from in vitro fertilisation (IVF) procedure.

Methods This retrospective cohort study was conducted at the Clinic for Gynaecology and Obstetrics, University Clinical Centre Tuzla, Bosnia and Herzegovina. Data from the delivery protocol were analysed over a five-year period between 1 January 2019 and 31 December 2023. A total of 257 deliveries from IVF pregnancies were analysed, constituting the study group, while the control group consisted of an equal number of women with spontaneously conceived pregnancies. The following data were analysed: baseline obstetrics and neonatal characteristics, and the presence of complications during pregnancy and delivery.

Results The average age of pregnant women was higher in the study compared to the control group (p=0.001). The average body weight and body length at birth were lower in the study group (p=0.001). The twin pregnancies were more frequent in the study group (p=0.0001). The largest number of primiparous women (p=0.0001) was recorded in the study group. A higher number of newborns with Apgar scores <7 at the first and fifth minutes was found in the study group (p=0.0001). There was higher prevalence of preterm births and cesarean section in the study group (p=0.0001). Fetal asphyxia and breech presentation were more prevalent in the study group (p=0.008 and p<0.0001).

Conclusion Pregnancies resulting from IVF were still riskier than those resulting spontaneously.

Key words: asphyxia neonatorum, cesarean section, premature birth, pregnancy, twin

INTRODUCTION

In modern times, due to the increased incidence of infertility (1), the number of couples requiring some form of assisted reproductive technology (ART) to achieve offspring has increased (2). ART includes *in vitro* fertilization (IVF), intrauterine insemination (IUI), egg donation and sperm donation, embryo donation, intracytoplasmic sperm injection (ICSI), cryopreservation (egg, sperm, and embryo freezing, surrogacy, preimplantation genetic testing (PGT -A) (2).

The standard IVF procedure involves the extracorporeal fertilization of sperm and egg through spontaneous interaction, embryo culture for 2 to 5 days, and embryo transfer into the uterus (3). It was reported that 10 to 13 million or more infants have been born from ART in the 40 years since the first ART-conceived infant was born in 1978 (4). A "good perinatal outcome" for newborns from pregnancies resulting from IVF was considered as a single pregnancy newborn born at term (>37 weeks of gestation) with a body weight >2500 grams (5). The success of the IVF procedure was related to the number of embryos transferred, with poorer outcome considered due to the increased prevalence of multiple pregnancies (6). Data showed that these pregnancies have an increased risk of poor perinatal outcome compared to pregnancies resulting from spontaneous conception (7).

In addition to the significantly higher risk of multiple pregnancies, IVF pregnancies also have an increased number of preterm births and newborns with low birth weight (8). Numerous studies have proven an increased risk for the occurrence of preeclampsia, gestational hypertension, placenta previa, and gestational diabetes (9).

There are numerous studies, systematic reviews and meta-analyses relating to this very interesting and researched topic (10,11). However, in our country, Bosnia and Herzegovina (B&H), research on infertility in general was scarce (only about the causes of infertility) (12); but no research on pregnancy outcomes after IVF procedures was found. Bosnian researcher investigated progesterone induced blocking factor taken in early pregnancy predicting the pregnancy

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outcome in women undergoing in vitro fertilization procedure (13). Also, reproductive characteristics and success rate of intracytoplasmic sperm microinjection in spinal cord injury infertile men were investigated (3). In addition, in B&H the difference in *Lactobacillus* abundance between age groups during ovarian stimulation in fresh *in vitro* fertilization (IVF) cycles (14) was investigated including an experience after the first 105 IVF cycles and how to make ART affordable (15).

The aim of this study was to determine the obstetrics outcome of pregnancies in women whose pregnancies resulted from IVF procedures. We want to investigate whether these are truly high-risk pregnancies, as obstetric scientific circles believe, or whether those are pregnancies with a normal favourable obstetric outcome and the usual complication prevalence, as in spontaneous pregnancies. The results of our study should be useful to a wider circle of obstetricians in B&H, and beyond, who encounter pregnancies resulting from IVF procedures in their daily practice.

PATIENTS AND METHODS

Patients and study design

This was a retrospective cohort study conducted at the Clinic for Gynaecology and Obstetrics, University Clinical Centre Tuzla, B&H. Data from the delivery protocol were analysed over a five-year period between 1 January 2019 and 31 December 2023. A total of 257 deliveries from IVF pregnancies were analysed, constituting the study group, while the control group consisted of an equal number of women with spontaneously conceived pregnancies. The control group was selected by taking the next pregnant woman in the delivery protocol following each IVF pregnancy case.

The Ethics Committee of the University Clinical Centre Tuzla approved the study.

Methods

The following data were analysed: average maternal age, parity (I, II, >III), number of newborns (singleton or multiple pregnancies), average birth weight of the newborns, average length of the newborns, Apgar score <7 after the first and fifth minutes, mode of delivery (vaginal or cesarean section), and the presence of complications during pregnancy and delivery. The complications analysed during pregnancy and delivery included: gestational hypertension, gestational diabetes, premature rupture of membranes, fetal asphyxia, breech presentation, placental abruption, and placenta previa, previous spontaneous abortion, preeclampsia).

Statistical analysis

For the statistical analysis of the data, descriptive statistics (mean value, standard deviation - SD), and percentage along with Student's t-test, Mann-Whitney U test, Chi-square test were employed; odds ratio was used in statistical data processing. A difference of $p<0.5$ was considered statistically significant.

RESULTS

The total number of deliveries from IVF pregnancies in five-year period were 257 (out of 14881 deliveries; 1.72%) (Table 1). A total number of newborns in the study group was 315.

Average age of pregnant women was higher in the study compared to the control group, 34.005.19 and 28.00±5.41, respectively ($p<0.001$) (Table 2).

The average body weight and body length at birth were in the study group statistically significantly lower compared to the control group, 2.990.00±774.41 and 3430±577.42, 53.00±4.69 and 55.00±3.30, respectively ($p<0.001$) (Table 2).

Twin pregnancies were more prevalent in the study group, in which one (0.38%) pregnant woman had triplets. Twin pregnancies were more frequent in the study compared to the control group, 57 (22.2%) and 3 (1.1%), respectively ($p<0.0001$) (Table 3).

The largest number of primiparous women, 226 (87.9%) ($p<0.0001$) was recorded in the study group, while in the control group there was the largest number of secondiparous women, 148 (57.6%) ($p<0.0001$) (Table 3).

It was found that a higher number of newborns with Apgar score <7 at the first and fifth minute was recorded in the study group, 76 (23.8%) and 37 (11.6%), respectively ($p<0.0001$). There was a higher prevalence of preterm births in the study group, and cesarean section deliveries were more frequent in the study group, 74 (28.8%) and 220 (85.6%), respectively ($p<0.0001$) (Table 3).

Table 1. Number of deliveries after in vitro fertilisation during the study period

Year	Total number of deliveries	Number (%) of deliveries (IVF)	Number of newborns
2019	3328	71 (2.1)	92
2020	2941	45 (1.5)	53
2021	2746	41 (1.5)	47
2022	2615	52 (1.9)	68
2023	2551	48 (1.8)	55
Total	14881	257 (1.72)	315

Table 2. Baseline maternal and neonatal characteristics of the study and control group

Characteristic	Study group		Control group		
	No of patients	Median±SD (min-max)	No of patients	Median±SD (min-max)	p
Maternal age (years)	257	34.00 ±5.19 (22.00-50.00)	257	28.00 ±5.41 (18.00-43.00)	<0.001
Birth weight (gr)	319	2.990.00 ±774.41 (300.00-2.990)	259	3430 ± 577.42 (1.000-3430)	<0.001
Birth length (cm)	319	53.00 ±4.69 (33.00-53.00)	259	55.00 ± 3.30 (34.00-55.00)	<0.001
Apgar score					
at first minute	319	8.00 ±1.49 (0.00-8.00)	259	9.00 ± 1.08 (4.00-9.00)	<0.001
at fifth minute	319	9.00 ±1.13 (0.00-9.00)	259	9.00 ± 0.61 (5.00-10.00)	<0.001

Table 3. Perinatal characteristics in the study and control group

Variable	No (%) of patients Study group	No (%) of patients Control group	p	Odds Ratio (95% CI)
Primiparous women	226 (87.9)	109 (42.4)	<0.0001	3.90 (6.31,15.52)
Gemels	57 (22.2)	3 (1.1)	<0.0001	24.13 (7.45,76.19)
Apgar score				
in first minute <7	76 (23.8)	30 (11.6)	<0.0001	3.18 (1.99,5.06)
in fifth minute <7	37 (11.6)	8 (3.1)	<0.0001	5.23 (2.39,11.48)
Preterm delivery	74 (28.8)	18 (7.0)	<0.0001	5.37 (3.10,9.31)
Cesarean Section	220 (85.6)	79 (30.7)	<0.0001	18.43 (11.43,29.60)

A higher number of pregnant women with hypertension was found in the study group, 41 (15.95%), without statistically significance difference between the groups (p=0.157). Diabetes and preeclampsia were found in equal numbers in both the study and control groups, three (1.16%) without statistical significance. Thrombophilia and previous spontaneous abortion were found in a higher number in the study group, without statistical significance (p=1.0). Premature rupture of membranes was present in a higher number in the study group compared to the control group, 50 (19.45%) and 43 (16.73%) without statistical significance (p=0.49) (Table 4).

Fetal asphyxia was found to be significantly more prevalent in the study group, 79 (30.73%), (p=0.008). Breech presentation was statistically more significant in the study group, 37 (14.39%), (p<0.0001). In the control group, there was a statistically significantly higher number of women who previously had cesarean section, 35 (13.61%), (p=0.02) (Table 4).

Table 4. Complications in pregnancy and delivery in the study and control group

Complication	No (%) of patients		p	Odds Ratio (95% CI)
	Study group	Control group		
Hypertension	41 (15.95)	29 (11.28)	0.157	-
Preeclampsia	3 (1.16)	3 (1.16)	1.0	-
Diabetes	3 (1.16)	3 (1.16)	1.0	-
Thrombophilia	17 (6.61)	7 (2.72)	0.05	-
Premature rupture of membranes	50 (19.45)	43 (16.73)	0.49	-
Previous spontaneous abortion	17 (6.61)	7 (2.72)	0.05	-
Previous cesarean section	18 (7)	35 (13.61)	0.02	0.48 (0.26, 0.87)
Fetal asphyxia	79 (30.73)	52 (29.23)	0.008	1.75 (1.17, 2.62)
Breech presentation	37 (14.39)	7 (2.72)	<0.0001	6.01 (2.62, 13.75)
Placental abruption	4 (1.55)	3 (1.16)	0.381	-
Placenta previa	1 (0.38)	3 (1.16)	0.617	-

DISCUSSION

The mechanisms involved in the association between IVF and poorer perinatal outcome were not entirely clear. One possible explanation was that perinatal complications may be due to the underlying cause of infertility itself, as numerous maternal factors associated with infertility also increase the risk of poorer perinatal outcome in women undergoing IVF (16). In our study 1.72% were pregnancies form IVF; in the study group the highest number were primiparous women. Our results were consistent with global studies that have found that women who give birth after IVF were mostly primiparous (17).

The age of the pregnant woman not only affects pregnancy outcome, but it is also closely related to infertility rates (18). Increasing age, the number of aneuploid oocytes also increases infertility. In women over 40 years of age, about 90% of oocytes are aneuploid (19). Older pregnant women were at higher risk of delivering low-birth-weight infants and experiencing preterm births (20). Our study showed that women undergoing IVF were significantly older, with average age of 34.0 years, compared to 28.0 years in the control group. This age was slightly higher compared to a study that reported average age of 31.87, even older women were found also in the control group, with an average age of 31.72 years (21). Numerous studies show that compared to fertile women, women who conceive through IVF are older, have more frequently preexisting chronic conditions, and have an increased risk of poorer perinatal outcome (22,23). We did not reduce the age rank for pregnant women (22-50) from the IVF group because we included all IVFs during the examined period; the reason is that one of the key characteristics and causes of infertility, especially in modern times, is the phenomenon of delayed motherhood, i.e. giving birth at a later age.

The average birth weight was significantly lower in women undergoing IVF, compared to women with spontaneously conceived pregnancies. Our data were similar to a study, where the average birth weight was higher in the fertile group, while in the IVF group, it was lower. The study also demonstrated an increased risk of delivering low-birth-weight infants and a higher prevalence of preterm births (24).

Women undergoing IVF have a higher percentage of preterm births, even when adjusting for maternal age and parity (25,26). The most common causes of preterm birth were cervical insufficiency and inflammatory processes, subsequently leading to premature rupture of membranes (26). A meta-analysis covering 25 studies found a twofold increased risk of preterm birth in singleton pregnancies following IVF compared to spontaneously conceived pregnancies (27). In our study, the percentage of preterm births among women with IVF was 28.79%, which was slightly lower compared to a study where it was 39.4% among primiparas and 42.2% among multiparas; low-birth-weight infants accounted for 36.8% of primiparas and 33.4% of multiparas. (21).

Apgar score <7 at the first minute was found in 24.12% of newborns, and Apgar <7 at the fifth minute was found in 11.74% of newborns in the study group. These values were higher compared to those from a study (24) where Apgar score <7 at the first minute was found in 4.9% of newborns and at the fifth minute in 1.3%. Fetal asphyxia was more common in the study group. The presence of Apgar score <7 in our study group can be attributed to the significantly lower average birth

weight of these newborns, and prematurity, which was also more frequent in the study group in our study.

Prematurity may also account for an increased number of breech presentations, which were more common in preterm births. Breech presentation was recorded in 14.39% pregnant women in our study. The IVF pregnancies held an increased risk of abnormal fetal head rotations, breech presentation and cesarean section (28,29). In our study a higher frequency of cesarean section of 89.10% was found in IVF pregnancies. This prevalence is significantly higher compared to a study, where the cesarean section rate was 58% (30).

The trend of increased cesarean sections rates was not only observed among spontaneous pregnancies but particularly among IVF pregnancies (31). Women who conceive through IVF are twice as likely to deliver by cesarean section. (27) The higher prevalence of cesarean section may be explained by the more frequent presence of placental insufficiency, preeclampsia, and other pregnancy complications. The increased prevalence of multiple pregnancies was one of the main reasons for the higher number of cesarean sections (26,32). Multiple pregnancies were associated with a higher risk of maternal complications (preeclampsia, gestational diabetes) and abnormal fetal presentation during delivery (26,32). An additional explanation for the increased number of cesarean sections could be the higher average maternal age, with many of these women experiencing their first pregnancy (32).

Twin pregnancies were a key factor for complications for both the mother and the newborn in pregnancies resulting from IVF. Twin pregnancies lead to numerous complications both during pregnancy and at delivery (26). There were more frequent abnormal positions of one or both fetuses, higher rates of prematurity, and, a greater likelihood of operative delivery (26). Many clinical studies recommend transferring only one embryo, which reduces the rate of twin pregnancies and thus improves perinatal outcome (33). In our study, there were 22.17% twin pregnancies and one (0.38%) pregnancy with triplets. Reportedly, a 20-fold increase in the prevalence of twin pregnancies in IVF pregnancies was found (21).

Among the recorded complications during pregnancy and delivery, hypertension was most frequently noted in our study. Since these were older pregnant women compared to the control group, they more frequently experience hypertension, whether it is chronic hypertension or hypertension that first appears during pregnancy. The risk of hypertensive disorders and preeclampsia in pregnancies following IVF is higher. In IVF pregnancies hypertension was present from 8.1% to 12.4% (34). Numerous studies have shown that preeclampsia results from improper placental vascularization, immune intolerance, endothelial cell activation, and excessive systemic inflammatory response (35).

IVF was an independent risk factor for developing gestational diabetes, with insulin resistance and hyperinsulinemia being implicated (1), as well as an increased prevalence of polycystic ovarian syndrome (PCOS) among patients undergoing IVF (36). In our study, diabetes was diagnosed in 1.16% of the pregnant women in the study group.

The risk of abnormal placentation involves several factors common to both fertile and infertile patients, such as advanced maternal age, endometrial damage, uterine scarring, and a short interval between a previous cesarean section and the current pregnancy (37). Many studies have shown increased frequency of abnormal placentation in women with ovulation stimulation and IVF procedures (38). An increased prevalence of placenta previa and placental abruption was reported (39).

Due to concerns about pathological conditions associated with thrombophilia, infertility patients undergoing IVF are now screened for thrombophilia prior to the procedure (40), and it can lead to thrombosis of uterine blood vessels, thereby causing placentation disorders (41). Thrombophilia was present in 6.61% of pregnant women in the study group.

Pregnant women undergoing IVF were at an increased risk of premature rupture of membranes. The cause was unknown, and it was one of the main causes of preterm birth (42,43). In our study, there was a slightly higher number of cases of premature rupture of membranes in the study group (no statistical significance).

The conducted study has certain limitations: it involves a five-year period and a small sample of IVF pregnancies, the data were obtained from the delivery protocols using available information, the study was conducted only in one institution. A study conducted in multiple institutions and over a longer time period would have greater significance.

Our study is the first of its kind in Bosnia and Herzegovina, it was conducted in one of the clinics that counts the largest number of births per year, so it is certainly a study with a fairly large sample. Through the study, we obtained results that may break the taboo and fear of obstetricians when it comes to pregnancies from IVF procedures.

In conclusion, pregnancies resulting from IVF are still riskier than those resulting spontaneously, which was confirmed by our study. We do not believe that the complications are a result of IVF, but rather that patients who undergo IVF and consequently their pregnancies, are more complex and have more risks and complications than pregnancies from natural conception, which we aimed to prove in our study.

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TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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