

Is in-vitro fertilization an independent risk factor for ROP?

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ABSTRACT

Purpose: To evaluate whether in-vitro fertilization (IVF) is an independent risk factor for retinopathy of prematurity (ROP) in premature infants.

Materials and Methods: Records of premature infants who underwent ROP examination between January 2011 and December 2022 were evaluated. In addition to ophthalmological findings, gender, gestational age (GA), birth weight (BW), mode of delivery (vaginal delivery/cesarean section), type of pregnancy (singleton/multiple), type of conception (spontaneous/IVF) and risk factors were noted and analyzed.

Results: Of the 500 infants included, 457 (91.4%) were conceived spontaneously and 43 (8.6%) were conceived through IVF. ROP was detected in 222 (44.4%) of the infants, of which 203 (40.6%) were conceived spontaneously and 19 (3.8%) were conceived through IVF. The incidence of severe ROP requiring treatment in these infants were 15.1% (n=69) and 23.3% (n=10), respectively. No statistically significant differences was found between the groups in terms of the incidence of any stage ROP and severe ROP requiring treatment. Although the incidence of multiple pregnancies was significantly higher in infants conceived through IVF ($p = 0.00$), no significant differences was found between pregnancy type and ROP. Additionally, the rate of ROP was found to be significantly higher in vaginal deliveries ($p=0.029$). In multiple regression analysis, the most significant variables associated with ROP were GA and BW.

Conclusion: IVF was not found to be an independent risk factor for ROP. However, it was found that ROP could develop at similar rates in both conceived through IVF and conceived spontaneously. Therefore, it would be appropriate to screen these infants carefully.

Keywords: Retinopathy of prematurity, in vitro fertilization, premature, spontaneous conception

INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative disease of the developing retina that can lead to visual impairment and even blindness in premature infants. It is a multifactorial disease and many risk factors such as gestational age (GA) and birth weight (BW), multiple pregnancies, prolonged parenteral nutrition, anemia, blood transfusion, prolonged mechanical ventilation, sepsis and assisted pregnancies are blamed.¹⁻⁵ In vitro fertilization (IVF), one of the assisted reproductive technologies (ART) used

in the treatment of infertility, has become an increasingly common method since 1978. The use of these technologies may result in an increased risk of premature birth due to the increase in multiple pregnancies. This situation also causes an increase in the number of babies diagnosed with ROP.⁶ There are many studies in the literature comparing IVF versus spontaneous conception.⁷⁻⁹ However, the effect of IVF on the frequency of ROP is controversial. While some studies indicate that IVF is an independent risk factor for ROP, some studies indicate that IVF alone does not

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affect the development of ROP, and that factors such as prematurity, BW and multiple births are also effective.^{4,10,11} Therefore, in current study, we evaluated whether IVF is an independent risk factor for ROP in premature infants.

MATERIAL AND METHODS:

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki, following Institutional Review Board approval (2023/09). All parents provided their informed consent. The records of five hundred infants examined for ROP between January 2011 and December 2022 were evaluated. In addition to the ophthalmological findings (ROP stages and zones, postmenstrual age (PMA) at examination, treatment options and PMA at treatment), gender, GA, BW, mode of delivery (vaginal delivery (VD)/ caesarean section (CS)), type of pregnancy (singleton/ multiple) and type of conception (spontaneous/ IVF) were collected.

Other neonatal (bronchopulmonary dysplasia (BPD; oxygen requirement >36 weeks PMA), small for gestational age (SGA; < 10th percentiles) patent ductus arteriosus (PDA, requiring treatment), duration of invasive mechanical ventilation (IMV, days), red blood cell (RBC) transfusions (≥ 2 times), chorioamnionitis, culture positive sepsis, necrotizing enterocolitis (NEC; \geq modified Bell's stage 2), and maternal risk factors (preeclampsia, gestational diabetes mellitus (GDM), prelabour rupture of the membranes (PROM)) were also noted. The infants were divided into two groups: spontaneous conception and conception through IVF. According to national guidelines, premature infants with GA <34 weeks and BW \leq 1700 g or GA \geq 34 weeks and BW >1700 g and premature infants with unstable clinical condition were screened for ROP.¹² After pupil dilation, dilated fundus examination of all infants was performed between 4 and 6 weeks. Ophthalmological findings were classified based on the International Classification of ROP, third edition (ICROP-3) criteria.¹³ Treatment decision for infants with severe ROP were made according to the "Early Treatment for ROP (ETROP)"¹⁴ and "Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP)"¹⁵ study criteria. Follow-up examinations were arranged according to the severity and course of ROP.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 25.0 was carried out for statistical analysis. The association between risk factors and ROP development was evaluated using univariate and multivariate logistic regression analysis. P-values of ≤ 0.05 was considered statistical significance.

RESULTS:

Of the 500 infants included, 457 (91.4%) were conceived spontaneously and 43 (8.6%) were conceived through IVF. The mean GA (weeks) and the mean BW (g) of the infants were 29.67 ± 2.63 (22-33 weeks) and 1405 ± 452.66 (525-2880 g), respectively. Although the GA of the infants in the IVF group was earlier and the BW was lower, no significant difference was detected between the groups ($p=0.807$ and $p=0.697$). The CS rate was significantly higher in the IVF group ($p=0.005$).

Overall, ROP was detected in 222 (44.4%) of the infants, of which 203 (40.6%) were conceived spontaneously and 19 (3.8%) were conceived through IVF. Of the spontaneously conceived infants, 82 (17.9%) had stage I ROP, 108 (23.6%) had stage II ROP, 6 (1.3%) had stage III ROP, and 69 of them (15.1%) progressed and required treatment. Again, among the infants conceived with IVF, 3 (6.9%) had stage I ROP, 9 (20.9%) had stage II ROP, 5 (11.6%) had stage III ROP, and 10 (23.2%) of them progressed and required treatment. Additionally, 2 (0.4%) of spontaneously conceived infants and 7 (16.2%) of conceived through IVF infants were treated with the diagnosis of aggressive ROP (A-ROP). No statistically significant difference was found between the groups in terms of the incidence of any stage ROP and severe ROP requiring treatment ($p=0.976$ and $p=0.161$). Demographic data and ophthalmic examination findings of the infants are shown in Table 1.

Of the 457 spontaneously conception infants, 120 (26.2%) were multiple pregnancies, 108 (23.6%) of which were twins and 12 (2.6%) were triplets. Again, of the 43 infants conceived through IVF, 38 (88.4%) were multiple pregnancies, 35 (81.4%) of which were twins and three (7%) were triplets. Although the incidence of multiple birth was significantly higher in infants conceived through IVF ($p=0.00$), no significant difference was found between ROP and pregnancy type ($p=0.076$). Additionally, the incidence

of ROP was significantly higher in vaginal deliveries (p=0.029). Incidence of ROP according to the type of conception, type of pregnancy and mode of delivery are shown in Table 2.

On the other hand, the incidence of maternal risk factors such as GDM and preeclampsia were found to be significantly higher in the spontaneously conceived infants (p=0.026 and p=0.016, respectively) (Table 3).

In univariate regression analysis, factors associated with the development of ROP were GA (p=0.00), BW (p=0.00),

mode of delivery (p=0.03), duration of IMV (p=0.00), RBC transfusion (p=0.00), total days on oxygen (p=0.00), BPD (p=0.00), PDA (p=0.00), chorioamnionitis (p=0.00), culture-positive sepsis (p=0.00) and PROM (0.00). Then, multivariate regression analysis was performed using these variables found to be significant. It was observed that, GA (OR, 0.63; 95% CI, 0.52-0.77; p=0.00) and BW (OR, 1.00; 95% CI, 1.00-1.00; p=0.00) were the most significant variables associated with ROP (Table 4).

Table 1. Demographic data and ophthalmic examination findings of the infants

		Spontaneous Conception (n=457)	Conception through IVF (n=43)	P - value
Gender	Female (n, %) Male (n, %)	203 (44.4 %) 254 (55.6%)	24 (55.8%) 19 (44.2%)	0.151*
Gestational age (weeks)	Mean ± SD (Range)	30 ± 3 (23-33)	29 ± 3 (23-33)	0.807**
BW (g)	Mean ± SD (Range)	1407 ± 446 (525-2880)	1383 ± 520 (595-2300)	0.697**
Mode of delivery				0.005**
Vaginal	n, %	71 (15.5%)	-	
Caesarean section	n, %	386 (84.5%)	43 (100%)	
Type of pregnancy				0.000**
Singleton	n, %	337 (73.7%)	5 (11.6%)	
Multiple	n, %	120 (26.3%)	38 (88.4%)	
PMA at examination (weeks)	Mean ± SD (Range)	34.70 ± 4.86 (28.43-84.71)	34.80 ± 4.22 (27.57-45.71)	0.716**
Any stage ROP (n, %)	ROP present	203 (44.4%)	19 (44.2%)	0.976**
	ROP absent	254 (55.6%)	24 (55.8%)	
Severe ROP (required treatment)	n, %	69 (15.1%)	10 (23.3%)	0.161**
LPC therapy	n, %	52 (75.4%)	7(70.0%)	0.716**
IVB therapy	n, %	17 (24.6%)	3(30.0%)	
Additional therapy	n, %	9 (2.0%)	2(4.7%)	0.252**
PMA at treatment (weeks)	Mean ± SD (Range)	36.83 ± 3.12 (31.43-45.86)	35.89 ± 3.64 (29.29-42.71)	0.606**

IVF, in vitro fertilization; SD, standart deviation; BW, birth weight; PMA, postmenstruel age; ROP, retinopathy of prematurity; LPC, laser photocoagulation; IVB, intravitreal bevacizumab; Bold, statistically significant values are highlighted

*Chi-square test

**Mann-Whitney U test

Table 2. Incidence of ROP according to the type of conception, type of pregnancy and mode of delivery

		ROP, (n=222)	No ROP, (n=278)	P - value
Type of conception				0.976*
Spontaneous	n, %	203 (44.4%)	254 (55.6%)	
IVF	n, %	19 (44.2%)	24 (55.8%)	
Type of pregnancy				0.076*
Singleton	n, %	161 (47.1%)	181 (52.9%)	
Multiple	n, %	61 (38.6%)	97 (61.4%)	
Mode of delivery				0.029*
Vaginal	n, %	40 (56.3%)	31 (43.7%)	
Caesarean section	n, %	182 (42.4%)	247 (57.6%)	

ROP, retinopathy of prematurity; IVF, in vitro fertilization; Bold, statistically significant values are highlighted
*Mann-Whitney U test

Table 3. Comparison of neonatal and maternal risk factors of the infants

		Spontaneous Conception (n=457)	Conception through IVF (n=43)	P - value
Neonatal morbidities				
BPD (oxygen requirement >36 weeks PMA)	n, %	131 (28.7%)	14 (32.6%)	0.591*
SGA < 10 th Percentile	n, %	50 (10.9%)	4 (9.3%)	0.741*
PDA (requiring treatment)	n, %	118 (25.8%)	13 (30.2%)	0.529*
Duration of IMV (days)	Mean ± SD	5.6 ± 17.0	6.8 ± 14.5	0.603*
RBC Transfusion (≥2 times)	n, %	70 (15.4%)	8 (18.6%)	0.574*
Chorioamnionitis	n, %	17 (3.7%)	1 (2.3%)	0.639*
Culture positive sepsis	n, %	79 (17.3%)	11 (25.6%)	0.176*
NEC (≥ stage 2)	n, %	2 (0.4%)	1 (2.3%)	0.125*
Total days on oxygen	Mean ± SD	26.0 ± 36.0	32.0 ± 39.0	0.650*
Maternal morbidities				
Maternal preeclampsia	n, %	73 (16.0%)	1 (2.3%)	0.016*
PROM	n, %	86 (18.8%)	12 (27.9%)	0.151*
GDM	n, %	38 (8.3%)	8 (18.6%)	0.026*

IVF, in vitro fertilization; SD, standart deviation; BPD, bronchopulmonary dysplasia; SGA, small for gestational age; PDA, patent ductus arteriosus; IMV, invaziv mechanical ventilation; RBC, red blood cell; NEC, necrotizing enterocolitis; PPROM, Preterm premature rupture of membranes, GDM, gestational diabetes mellitus
*Mann-Whitney U test

Table 4. Logistic regression analysis of risk factors related with ROP development

	Univariable analysis			Multivariable analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Gender	0.84	0.59-1.20	0.35	-	-	-
GA	0.48	0.42-0.54	0.00	0.63	0.52-0.77	0.00
BW	1.00	1.00-1.00	0.00	1.00	1.00-1.00	0.00
C/S	0.57	0.34-0.95	0.03	0.84	0.38-1.85	0.67
Multiple pregnancy	1.41	0.96-2.08	0.08	-	-	-
IVF	0.99	0.53-1.86	0.98	-	-	-
IMV	1.16	1.10-1.22	0.00	1.06	0.98-1.13	0.14
RBC Transfusion	11.79	5.90-23.57	0.00	0.50	0.17-1.52	0.22
Total days on oxygen	1.05	1.04-1.06	0.00	1.01	0.99-1.03	0.33
BPD	9.95	6.21-15.94	0.00	0.92	0.33-2.52	0.87
PDA	6.53	4.13-10.32	0.00	0.63	0.30-1.33	0.22
Chorioamnionitis	6.64	1.90-23.25	0.00	3.59	0.81-15.87	0.09
Sepsis	5.94	3.48-10.15	0.00	1.58	0.74-3.40	0.24
NEC	2.52	0.23-27.95	0.45	-	-	-
SGA	1.00	0.57-1.77	0.99	-	-	-
Preeclampsia	0.83	0.50-1.37	0.47	-	-	-
GDM	0.64	0.34-1.21	0.17	-	-	-
PROM	2.00	1.28-3.13	0.00	0.90	0.45-1.77	0.75

Variables with p<0.05 in univariate analysis were included in multivariate regression
 Bold, statistically significant values are highlighted
 OR, odds ratio; CI, confidence interval; ROP, retinopathy of prematurity; GA, gestational age; BW, birth weight; C/S, caesarean section; IVF, in-vitro fertilization; IMV, invasiv mechanical ventilation; RBC, red blood cell transfusions, ≥ 2 times; BPD, bronchopulmonary dysplasia oxygen requirement >36 weeks PMA; PDA, patent ductus arteriosus requiring treatment; NEC, necrotizing enterocolitis; SGA, small for gestational age; GDM, gestational diabetes mellitus; PROM, prelabour rupture of the membranes.

DISCUSSION:

Today, with the increase in infertility, IVF, one of the ART technologies, is becoming more accessible and its use is increasing. IVF is proposed to increase ROP indirectly through prematurity, low BW, and multiple gestation, which are well established risk factors for ROP. Additionally, it can contribute to abnormal retinal vascular development by affecting postpartum angiogenic regulation.^{1,2,6}

McKibbin and Dabbs, who evaluated the relationship between assisted pregnancy (AC) and ROP in 1996, noted that 16.5% (44 infants) of the infants were born after AC. They stated that while ROP was detected at any stage in 10

of these infants, 3 of them progressed to stage III ROP and 2 of them required treatment because they progressed to threshold disease. However, the type of AC of these infants is not specified. As a result, it has been stated that since AC treatment may be an effective factor in the progression of ROP and the need for treatment, the increased use of these treatment methods may lead to an increase in the demand for ROP screening programs.⁸ In another study conducted in the same center, Funnell et al. reported that 60.3% (n=477) of the infants were singletons, 36.9% (n=292) were twins and 1.5% (n=12) were triplets, and 265 of the infants were born as a result of AC techniques. They also stated that ROP screening was required in 4.2% of all AC births (11 infants),

but ROP was not detected in any infants. As a result, they noted that, according to the McKibbin study, the decrease in the percentage of AC infants requiring ROP screening may be due to the decrease in multiple birth rates.⁷

Although there are various studies on the effect of ART, particularly IVF on ROP, it is not yet clear whether it constitutes an independent risk factor for ROP. In the study conducted by Frilling et al., in which they evaluated infants, 204 of whom were conceived naturally and 159 of whom were conceived with AC (IVF or IVF combined with drug therapy), it was stated that 43.8% of the infants (159 infants) developed ROP and that the most important factors in the development of ROP were GA and BW, but not AC.⁴ Dabir et al. reported that although advanced ROP was more common in spontaneous pregnancy, there was no significant difference between the groups in terms of the development of any stage of ROP ($p=0.57$) and the stages of ROP ($p=0.24$). It has also been stated that IVF is not an independent factor in the development of ROP. Additionally, risk factors such as RDS, oxygen therapy and sepsis were reported to be significantly higher in the spontaneous pregnancy group ($p<0.05$).⁵ Barker et al. reported that although the incidence of ROP was higher in infants born with ART (IVF, intracytoplasmic sperm injection, and drug therapy), there was no significant difference between infants conceived naturally and those born with ART.⁹ A study conducted in our country in 2016 with consecutive premature triplets born both naturally and through ART indicated that there was no relationship between the presence of ROP and the type of pregnancy.¹⁶ Alsammahi et al. reported that the incidence of ROP was significantly higher in the ART group (e.g. IVF) ($p=0.045$) and in multiple births ($p=0.033$), although ART alone was not a risk factor in multiple births. In addition, infant factors such as blood transfusion, intraventricular hemorrhage, sepsis and PDA, and maternal factors such as PROM and antenatal steroid treatment were determined to be significantly associated with ROP.¹⁷ In a study conducted by Uberos et al. in 2024, which also supports our study, it was found that IVF was not associated with an increased ROP incidence of very low BW infants.¹⁸

In contrast to previous studies, Watts and Adams found that 41.6% of infants born with IVF progressed to stage III ROP, compared to only 9.37% in naturally conceived

infants. IVF appears to be the main risk factor in the development of threshold ROP and that attention should be paid to the screening of these infants.¹⁰ Similarly, Gao et al reported a significant association between IVF and stage 3 ROP, but this association was more common in singleton pregnancies.¹⁹ Chan et al. found that ART, as well as GA, were independent risk factors for the development of ROP requiring treatment. They also showed in multifactorial analysis that risk factors such as mechanical ventilation, sepsis, BPD and NEC are not effective factors in the development of ROP requiring laser treatment.²⁰

In the present study, the incidence of any stage ROP was similar between infants conceived with IVF (44.2%) and those conceived spontaneously (44.4%). No significant difference was found between the groups in terms of any stage of ROP ($p=0.976$) and severe ROP ($p=0.161$). While the incidence of multiple births was found to be significantly higher in infants conceived through IVF, the incidence of ROP was found to be higher in singleton pregnancies. However, no significant difference was found between pregnancy type and ROP ($p = 0.076$). When all factors were evaluated, it was observed that the independent risk factors were only GA and BW, but not IVF. We also observed a significant association between ROP and maternal preeclampsia and GDM ($p= 0.016$, $p=0.026$). In the literature, a meta-analysis including 13 cohort studies evaluated the relationship between hypertension and ROP during pregnancy, but no clear conclusion was reached.²¹ Similarly, no clear relationship was detected between maternal DM and ROP.²²

It would be appropriate to consider certain limitations when evaluating the study. First, the available data are limited due to its retrospective nature. Second, although the number of infants included in the study was not small, the low number of infants conceived with IVF may have caused us not to detect a significant difference between the groups. Despite these limitations, our study is one of the few in our country to cover a period of more than 10 years, and our results may contribute to the improvement of national screening guidelines.¹²

CONCLUSION

In conclusion, IVF was not found to be an independent risk factor for ROP. However, it was found that ROP could de-

velop at similar rates in both conceived through IVF and conceived spontaneously. Therefore, it would be appropriate to screen these infants carefully.

DISCLOSURE OF INTEREST INFORMATION

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