Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Association between assisted reproductive technology and advanced retinopathy of prematurity

This article was published in the following Dove Press journal:
Clinical Ophthalmology
25 November 2010
Number of times this article has been viewed

RV Paul Chan[1]
Yoshihiro Yonekawa[1]
Margaux A Morrison[2,3]
Grace Sun[1]
Ryan K Wong[1]
Jeffrey M Perlman[4]
Michael F Chiang[5,6]
Thomas C Lee[7]
M Elizabeth Hartnett[3]
Margaret M DeAngelis[2,3]

[1]Department of Ophthalmology, Weill Cornell Medical College, New York; [2]Ocular Molecular Genetics Institute, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts; [3]University of Utah School of Medicine, Moran Eye Center, Salt Lake City, Utah; [4]Department of Pediatrics, Weill Cornell Medical College, New York; Departments of [5]Ophthalmology and [6]Biomedical Informatics, Columbia University College of Physicians and Surgeons, New York; [7]The Vision Center, Children's Hospital Los Angeles, California, USA

Correspondence: Margaret M DeAngelis
Department of Ophthalmology and Visual Sciences, University of Utah School of Medicine, John A Moran Eye Center, 65 North Medical Drive, Salt Lake City, Utah 84132, USA
Tel +1 801 213 4052
Fax +1 801 581 5335
Email margaret.deangelis@utah.edu

Purpose: To investigate the associations between assisted reproductive technology (ART) and severe retinopathy of prematurity (ROP) requiring treatment.

Methods: Retrospective analyses of inborn preterm infants screened for severe ROP at the Weill Cornell Medical Center Neonatal Intensive Care Unit at the New York-Presbyterian Hospital by single factor logistic regression and multifactor models.

Results: Of 399 ethnically diverse infants, 253 were conceived naturally and 146 by ART. Eight (3.16%) patients conceived naturally, and 11 (7.53%) with ART required laser treatment. In multifactor analyses, significant risks for severe ROP requiring treatment included both gestational age (odds ratio [OR] 0.34; 95% confidence interval [CI] 0.23–0.52; $P < 0.001$) and ART ([OR] 4.70; [CI], 1.52–4.57; $P = 0.007$).

Conclusions: ART is associated with severe ROP requiring treatment in this cohort. This is the first report that demonstrates a statistically significant association between ART and severe ROP requiring treatment in infants in the US.

Keywords: retinopathy of prematurity, low birth rate, blindness, assisted reproductive technology

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retina that accounts for over 50,000 blind children worldwide. In the US, severe ROP is a major cause of childhood blindness and is the leading cause of blindness in premature babies.[1–3]

Historically, two epidemics of severe ROP have been described in industrialized countries. The first occurred in the 1940s and 1950s and was largely attributed to unmonitored, supplemental oxygen at birth. Technologic advances permitting the regulation and monitoring of oxygen led to a reduction in the incidence of ROP. A second rise in acute ROP occurred in the 1970s in association with improved survival of premature infants born at young gestational ages and low birth weights.[3] With ongoing advances in neonatal care, there has been an increase in the survival of extremely low birth weight infants (less than 1000 g).[3,4] Also, preterm birth is on the rise in many regions in the US and worldwide. These factors add to the likelihood of increased incidence of ROP.

Both the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) and the Early Treatment for Retinopathy of Prematurity (ET-ROP) studies provided an understanding of the natural history of ROP and evidence that treatment of the peripheral avascular retina in severe forms of ROP was associated with better anatomic and functional results.[5,6] However, despite appropriate and timely management, ROP still causes

visual impairment and blindness in many infants in the US, particularly those born at extremely low birth weights.[7]

Prematurity and very low birth weight have been linked to assisted reproductive technology (ART), partly because of multiple births. In the US, the number of babies conceived through ART is increasing.[8] Reports of the impact of ART on the incidence or progression of ROP have been inconsistent in the past. Some studies found associations between ART and ROP, whereas more recent studies suggest that ART alone was not associated with ROP, but rather that other known risk factors, such as young gestational age, low birth weight, or multiple births, possibly accounted for some of the previously reported associations.[9–13] Given the lack of consistency in the published data, and specifically because previous studies had not been reported in patient samples in the US, we were interested in the role of ART in the development of severe ROP. Therefore, we explored associations between ART and ROP requiring treatment in a single neonatal intensive care setting.

Methods

Subjects

Institutional review board approval was obtained to perform a retrospective review of consecutive inborn infants at the Weill Cornell Medical Center Neonatal Intensive Care Unit at the New York-Presbyterian Hospital from June 2002 to August 2007. The screening criteria at Weill Cornell Medical Center Neonatal Intensive Care Unit for ROP during the time of this study were gestational age <32 weeks and/or birth weight <1500 g, with first examinations at 31 weeks postgestational age or 4–6 weeks after birth. Also included in screening beyond these criteria were infants on high oxygen who had unstable courses in the Neonatal Intensive Care Unit or for whom a consultation was requested by a neonatologist. Infants were divided into two groups, ie, those conceived naturally (natural conception group) or by ART. Infants were also stratified into those born at birth weights <1000 g and those born at 1000–1500 g. Included in the review were all patients born within Weill Cornell Medical Center, without pre-existing congenital disorders, and who had survived throughout the hospital stay. White race has been found to be an independent risk factor for developing severe ROP,[14–17] and efforts were made to recruit all ethnicities and races. Information abstracted from records included birth weight, gestational age, gender, race, type of pregnancy, complications of prematurity, ventilation, and duration of oxygen exposure. Zone and stage of ROP were documented in accordance with the International Classification for ROP.[18] Examinations were performed by one of two examiners (RVPC and TCL).

Statistical analysis

Statistical analyses were performed using SAS 9.0 (SAS Institute, Cary, NC). Initially, single factor logistic regression was performed on all risk factors (see Table 1) individually to test their association with ROP needing laser treatment. A multifactor model was then constructed using risk factors that were suggestive of association with need for laser treatment, defined as $P < 0.1$ in the single factor analysis. In order to create the most parsimonious statistical model predictive of the need for laser treatment of ROP, a second multifactor model was constructed using risk factors that remained significant after the initial multifactor model, as performed in previous epidemiologic papers.[19] The Students' *t*-test was used to determine if there was a significant difference in mean birth weight between the natural conception and ART groups, and the Mann–Whitney *U* test was used to analyze mean gestational ages between infants requiring laser in the two groups. A P value of ≤ 0.05 was considered statistically significant. Tests for interactions between variables were also performed in SAS.[20]

Results

Study population

The patient population comprised 399 infants, of whom 47 were black, 252 white, 50 Hispanic, 39 Asian, five Native American, and six infants of other races. Of these 399 infants, 253 were in the natural conception group and 146 were in the ART group. Of the infants born through natural conception, 38 were black, 133 white, 44 Hispanic, 32 Asian, two Native American, and four infants of other races. Of those naturally conceived, 128 were male and 125 female, and there were 157 (62%) singletons and 96 (38%) multiplets. Mean gestational age at birth was 29.00 ± 2.14 weeks. In the ART group, nine infants were black, 119 white, six Hispanic, seven Asian, three Native American, and two infants of other race. Of infants in the ART group, 81 (55%) were male and 65 (45%) female, and there were 18 (12%) singletons and 128 (88%) multiplets. Mean gestational age was 29.14 ± 2.00 weeks (Table 1).

The mean birth weight for all 399 infants was 1207.5 ± 351.1 g. There was a significant difference between mean birth weight of infants in the natural conception group compared with those in the ART group (1255.8 ± 362.2 g and 1179.6 ± 342.1 g, respectively, $P = 0.04$, Table 2).

Risk of ROP requiring treatment

Eight (3.16%) of 253 infants in the natural conception group and 11 (7.53%) of 146 infants in the ART group developed severe ROP that required laser treatment. Of the 19 infants

Table 1 Patient characteristics

	All	Natural conception	ART
Total patients	399 (100.00%)	253 (63.41%)	146 (36.59%)
Mean BW in grams (SD)	1207.47 (351.07)	1179.57 (342.14)	1255.81 (362.16)
Mean GA in weeks (SD)	29 1/7 (2 1/7)	29 (2 1/7)	29 1/7 (2)
Gender			
Male	209 (52.38%)	128 (50.59%)	81 (55.48%)
Female	190 (47.62%)	125 (49.41%)	65 (44.52%)
Race			
Black	47 (11.78%)	38 (15.02%)	9 (6.16%)
White	252 (63.16%)	133 (52.57%)	119 (79.87%)
Hispanic	50 (12.53%)	44 (17.39%)	6 (4.03%)
Asian	39 (9.77%)	32 (12.65%)	7 (4.70%)
Native American	5 (1.25%)	2 (0.79%)	3 (2.01%)
Other	6 (1.50%)	4 (1.58%)	2 (1.34%)
Unknown	0 (0.00%)	0 (0.00%)	0 (0.00%)
Multiple births			
Singleton	175 (43.86%)	157 (62.06%)	18 (12.33%)
Multiplets	224 (56.14%)	96 (37.94%)	128 (87.67%)
Twins	188 (47.12%)	92 (36.36%)	96 (65.75%)
Triplets	32 (8.02%)	4 (1.58%)	28 (19.18%)
Quadruplets	4 (1.00%)	0 (0.00%)	4 (2.74%)
Mean MA in years (SD)	33.21 (6.00)	31.9 (5.57)	35.46 (6.00)
Details of ROP treatment			
Lasered	19 (4.76%)	8 (3.16%)	11 (7.53%)
Post-GA at laser in weeks	36	35 4/7	36 2/7
Complications			
MV	134 (33.58%)	84 (33.20%)	50 (34.25%)
Sepsis	77 (19.30%)	53 (20.95%)	24 (16.44%)
IVH	59 (14.79%)	42 (16.60%)	17 (11.64%)
BPD	17 (4.26%)	13 (5.14%)	4 (2.74%)
NEC	18 (4.51%)	13 (5.14%)	5 (3.42%)

Abbreviations: ART, assisted reproductive technology; GA, gestational age; BW, birth weight; SD, standard deviation; MA, maternal age; MV, mechanical ventilation defined as ≥96 hours; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

who required laser treatment, 7 (37%) were singletons and 12 (63%) were multiplets. In the natural conception group, four (50%) of eight infants treated with laser were singletons and four (50%) were multiplets (all twins). In the ART group, three (27%) were singletons, and eight (73%) were multiplets (six twins and two triplets). In single factor analysis, ART was a modest risk factor for requiring laser treatment for ROP when compared with natural conception ($P = 0.06$, Table 3). When the subject population included only those infants born under 1500 g and was stratified by birth weight, ART was found to be a significant factor associated with severe ROP requiring treatment, particularly for those infants born less than 1000 g (odds ratio [OR] 3.57; confidence interval [CI] 1.24–10.25; $P = 0.02$, Table 4). Table 3 also shows that birth weight, mechanical ventilation ≥96 hours, sepsis, or bronchopulmonary dysplasia (factors that were $P \leq 0.1$ in single factor analysis) when included in the initial multifactor analysis (Table 3), were not statistically significant in the presence of the other factors. In an initial multifactor model, gestational age, ART, and necrotizing enterocolitis remained significant after controlling for the effects of birth weight, mechanical ventilation, sepsis, and bronchopulmonary

Table 2 Differences in characteristics of infants born by assisted reproductive technology and natural conception

Category	ART	Natural conception	*t*-test *P* value[a]
Mean BW in grams (SD)	1255.81 (362.16)	1179.57 (342.14)	0.04
BW in lasered children in grams (SD)	780.00 (130.09)	757.13 (147.37)	0.72
Mean age for laser in weeks (SD)	36.26 (2.17)	35.54 (3.05)	0.56

Note: [a]Students' *t*-test was used to determine if there was a significant difference between the two values.
Abbreviations: ART, assisted reproductive technology; BW, birth weight; SD, standard deviation.

Table 3 Logistic regression analysis of risk factors for retinopathy of prematurity requiring laser treatment (n = 399)

Risk factor	Single factor analysis			Multifactor analysis 1[a]			Multifactor analysis 2[b]		
	OR	95% CI	*P* value	Adj OR	95% CI	*P* value	Adj OR	95% CI	*P* value
GA	0.38	0.26–0.54	<0.001	0.42	0.23–0.78	0.003	0.34	0.23–0.52	0.001
BW	0.99	0.991–0.996	<0.001	1.00	0.99–1.00	0.19	–	–	–
ART	2.50	0.98–6.35	0.06	5.55	1.63–18.83	0.006	4.70	1.52–14.57	0.007
Female gender	0.79	0.31–2.01	0.62	–	–	–	–	–	–
Singleton	0.74	0.28–1.91	0.53	–	–	–	–	–	–
Maternal age	1.03	0.96–1.11	0.43	–	–	–	–	–	–
MV	8.19	2.66–25.21	<0.001	0.92	0.21–3.98	0.91	–	–	–
Sepsis	2.58	0.98–6.78	0.06	0.50	0.14–1.72	0.27	–	–	–
IVH	1.58	0.50–4.92	0.43	–	–	–	–	–	–
BPD	4.90	1.30–18.79	0.02	2.53	0.47–13.49	0.27	–	–	–
NEC	4.56	1.20–17.37	0.03	6.25	1.06–36.69	0.04	5.23	0.92–29.80	0.06

Notes: [a]Multivariate model was constructed using risk factors that were at least moderately associated with need for laser treatment, defined as $P < 0.1$ in the univariate analysis; [b]Second multivariate model was constructed by using risk factors that remained significant in the first multivariate model.

Abbreviations: OR, odds ratio; CI, confidence interval; Adj, adjusted; GA, gestational age; BW, birth weight; ART, assisted reproductive technology; MV, mechanical ventilation defined as ≥96 hours; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis.

dysplasia. However, in a more stringent multifactor model including only ART, necrotizing enterocolitis, and gestational age, both gestational age and ART were significantly associated with severe ROP needing treatment (OR 0.34, CI 0.23–0.52; $P < 0.001$; and OR 4.70, CI 1.52–14.57; $P = 0.007$, respectively). To test for interaction between ART and birth weight, an interaction term was included in the model with gestational age and ART. The logistic regression showed no interaction between ART and gestational age ($P = 0.45$), suggesting that both are independent risk factors for severe ROP (data not shown).

Discussion

The aim of this study was to explore associations between ART and severe ROP requiring treatment. Using multifactor analysis, the key finding was that, regardless of birth weight, ART was associated with a nearly five-fold increased risk of severe ROP requiring treatment after controlling for potential confounders (OR 4.70, CI 1.52–14.57; $P = 0.007$). Gestational age was also a significant risk factor, and both gestational age and ART appear to be independent risk factors associated with risk of severe ROP requiring laser.

Previous studies have reported conflicting results regarding the relationship between ART and severe ROP. For example, Friling et al failed to demonstrate an association between the two,[13] whereas Watts and Adams found an association between the development of threshold severe ROP and ART, specifically in vitro fertilization, although statistical significance was not achieved.[11] Watts and Adams noted that for infants developing Stage 3 severe ROP, those conceived through in vitro fertilization were born at older gestational ages on average and at heavier birth weights than infants who received other forms

Table 4 Single factor logistic regression analysis of risk factors for retinopathy of prematurity requiring laser treatment, stratified by birth weight

Risk factor	BW < 1000 g (n = 112)			BW < 1500 g (n = 312)		
	OR	95% CI	*P* value	OR	95% CI	*P* value
GA	0.45	0.28–0.73	0.001	0.388	2.67–0.57	<0.001
ART	3.57	1.24–10.25	0.02	2.74	1.07–7.02	0.04
Female gender	0.37	0.13–1.04	0.06	0.74	0.29–1.90	0.53
Singleton	0.35	0.12–1.02	0.05	0.63	0.24–1.64	0.35
Maternal age	1.02	0.93–1.12	0.66	1.04	0.96–1.13	0.35
MV	4.58	1.24–16.87	0.02	6.48	2.09–20.04	0.001
Sepsis	0.95	0.32–2.77	0.92	1.96	0.74–5.17	0.17
IVH	0.70	0.21–2.32	0.56	1.34	0.42–4.17	0.63
BPD	2.04	0.50–8.31	0.32	4.04	1.04–15.62	0.04
NEC	3.54	0.79–15.76	0.10	4.04	1.04–15.62	0.04

Abbreviations: BW, birth weight; OR, odds ratio; CI, confidence interval; GA, gestational age; ART, assisted reproductive technology; MV, mechanical ventilation defined as ≥96 hours; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis.

of ART.[11] Minasion and Fielder also reported that severe ROP can affect larger and more mature babies conceived through in vitro fertilization compared with those who are not.[10] We observed a modestly significant increase in mean birth weight for infants born through ART than those through natural conception ($P = 0.04$). Although the mean gestational age at birth was similar between the two groups, the mean time of treatment for severe ROP was approximately one week later in the ART group (36 2/7 weeks) than in the natural conception group (35 4/7 weeks). Both of these findings, along with the lack of a significant interaction between ART and gestational age, suggest that a subset of infants born through ART is susceptible to severe ROP regardless of the effect of gestational age, postgestational age, or birth weight. These differences in weight and gestational age between babies requiring treatment for severe ROP in the ART and natural conception groups may also have implications for screening criteria. Although the CRYO-ROP study provided information on the natural history of infants having severe ROP,[5] the natural history of severe ROP for infants born through ART may follow a different course.

ART has been associated with multiple births,[21] as has severe ROP. In the US, the number of multiple births has risen dramatically over the past two decades, and much of this trend has been attributed to the increased use of ART.[8,21] In our study, there was a larger number of multiplets in the ART group, and it was the multiplets who required laser more often. The numbers of infants requiring laser treatment in each group was small (n = 8 versus n = 11), and we cannot conclude that multiple births was not a factor if a larger sample were studied.[21–23] However, there are conflicting reports in the literature. Some reports have noted an increase in threshold severe ROP with multiple births, while others have not. Blumenfeld et al reported no significant difference in severe ROP incidence between singleton and multiple gestation babies.[24] However, Friling et al found a trend that singletons had more severe ROP than multiplets, but after logistic regression analysis, the factors of low birth weight and gestational age were found to be the primary risk factors for severe ROP.[13]

Schaffer et al analyzed the CRYO-ROP study population and reported an increased risk of threshold severe ROP in infants born with low birth weight, young gestational age, white race, and of multiple births.[16] Given that the majority of infants born through ART in the US are white,[25–27] the racial disparity may influence the results when analyzing the risk of ART on severe ROP. Previous studies that examined the association between severe ROP and ART failed to include race as a major consideration, although infants who develop severe ROP are more often white than black.[9–13] In our population, the number of black infants in the ART group was too small to derive meaningful conclusions, although when tested as a risk factor, black race was not significant ($P = 0.96$, data not shown). Furthermore, no black babies required laser treatment. The failure to control for race may cause a systematic bias, because racial differences have been noted in the incidence of severe ROP among infants <1251 g at birth,[14–17] however, black race was not significant in this study. Regardless, the conclusions drawn from our study should only be applied to nonblack infants due to the fact that no black infants required laser treatment in this study.

Several factors should also be considered when interpreting the results of this study. First, given the retrospective nature of this study, our analysis was limited in controlling for potential confounders. We collected data on the presence of sepsis, mechanical ventilation time ≥ 96 hours, intraventricular hemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis. Multifactor logistic regression analysis was then performed to control for the effects of these potential confounders with development of advanced severe ROP requiring treatment. Second, we were unable to look at specific maternal records in depth, and as a result we were unable to determine the type of assisted conception used or determine whether potential confounding risks were present, such as preeclampsia or new-onset maternal gestational hypertension.[28] Watts and Adams had previously addressed this issue, stating that in vitro fertilization specifically was directly related to an increased risk of severe ROP.[11] It has also been suggested that in vitro fertilization is associated with ocular disorders, such as retinoblastoma[29] and that ART may predispose children to certain genetic abnormalities.[30] Previously, 70% of the genetic variance in severe ROP has been reportedly attributed to genetic factors.[31] Therefore, an association between ART and severe ROP may point to a genetic predisposition in these infants and warrant additional study. At this point, the question remains as to whether ART predisposes infants to specific ocular abnormalities. Future studies should be prospective and investigate the type of ART methods used, the number of treatments, and other fertility drugs given to the mother.

In conclusion, the data presented here suggest an association between an ART population and severe ROP requiring treatment in nonblack infants. To the best of the authors' knowledge, this is the first study that has found a statistically significant association between ART and severe ROP requiring treatment in the US. The causes for this association, however, are unclear, and future studies are warranted to examine factors associated with ART.

Acknowledgments

This study was supported by the St. Giles Foundation, New York, NY (RVPC), a Departmental Grant from Research to Prevent Blindness, New York, NY (RVPC), a Career Development Award from Research to Prevent Blindness, New York, NY (MFC), Boston University School of Public Health Merit Scholarship (MAM), March of Dimes 6-FY08-206 (MEH), and NIH/NEI grants EY19474 (MFC), EY015130 (MEH), and EY014458 (MMD).

Disclosure

The authors have no commercial, proprietary, or financial interest in any of the products or companies described in this article. MFC is an unpaid member of the Scientific Advisory Board for Clarity Medical Systems (Pleasanton, CA).

References

1. Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A. Retinopathy of prematurity in middle-income countries. *Lancet*. 1997;350(9070):12–14.
2. Gilbert C, Foster A. Childhood blindness in the context of VISION 2020 – the right to sight. *Bull World Health Organ*. 2001;79(3):227–232.
3. Gilbert C. Retinopathy of prematurity: A global perspective of the epidemics, population of babies at risk and implications for control. *Early Hum Dev*. 2008;84(2):77–82.
4. Flynn JT, Chan-Ling T. Retinopathy of prematurity: Two distinct mechanisms that underlie zone 1 and zone 2 disease. *Am J Ophthalmol*. 2006;142(1):46–59.
5. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter Trial of Cryotherapy for Retinopathy of Prematurity; ophthalmological outcome at 10 years. *Arch Ophthalmol*. 2001;119(8):1110–1118.
6. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol*. 2003;121(12):1684–1696.
7. Repka MX, Tung B, Good W, et al. Outcome of eyes developing retinal detachment during the Early Treatment for Retinopathy of Prematurity Study (ET-ROP). *Arch Ophthalmol*. 2006;124(1):24–30.
8. Wright VC, Chang J, Jeng G, Macaluso M; Centers for Disease Control and Prevention (CDC). Assisted reproductive technology surveillance – United States, 2005. *MMWR Surveill Summ*. 2008;57(5):1–23.
9. Funnell CL, Dabbs TR. Assisted conception and retinopathy of prematurity: 8-year follow-up study. *Eye (Lond)*. 2007;21(3):383–386.
10. Minasian M, Fielder A. IVF babies with severe retinopathy of prematurity at higher gestational age and birth weight: Implications of changing screening criteria. *Br J Ophthalmol*. 2005;89(8):1066.
11. Watts P, Adams GG. In vitro fertilisation and stage 3 retinopathy of prematurity. *Eye (Lond)*. 2000;14(3):330–333.
12. McKibbin M, Dabbs TR. Assisted conception and retinopathy of prematurity. *Eye (Lond)*. 1996;10(4):476–478.
13. Friling R, Axer-Siegel R, Hersocovici Z, Weinberger D, Sirota L, Snir M. Retinopathy of prematurity in assisted versus natural conception and singleton versus multiple births. *Ophthalmology*. 2007;114(2):321–324.
14. Palmer EA, Flynn JT, Hardy RJ, et al. Incidence and early course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Ophthalmology*. 1991;98(11):1628–1640.
15. Saunders RA, Donahue ML, Christmann LM, et al. Racial variation in retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Arch Ophthalmol*. 1997;115(5):604–608.
16. Schaffer DB, Palmer EA, Plotsky DF, et al. Prognostic factors in the natural course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Ophthalmology*. 1993;100(2):230–237.
17. Yang MB, Donovan EF, Wagge JR. Race, gender, and clinical risk index for babies (CRIB) score as predictors of severe retinopathy of prematurity. *J AAPOS*. 2006;10(3):253–261.
18. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol*. 2005;123(7):991–999.
19. DeAngelis MM, Lane AM, Shah CP, Ott J, Dryja TP, Miller JW. Extremely discordant sib-pair study design to determine risk factors for neovascular age-related macular degeneration. *Arch Ophthalmol*. 2004;122(4):575–580.
20. DeAngelis MM, Ji F, Kim IK, et al. Cigarette smoking, CFH, APOE, ELOVL4, and risk of neovascular age-related macular degeneration. *Arch Ophthalmol*. 2007;125(1):49–54.
21. Luke B, Martin JA. The rise in multiple births in the United States: Who, what, when, where, and why. *Clin Obstet Gynecol*. 2004;47(1):118–133.
22. Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with use of assisted reproductive technology. *N Engl J Med*. 2002;346(10):731–737.
23. Hansen M, Kurinczuk JJ, Bower C, Webb S. The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. *N Engl J Med*. 2002;346(10):725–730.
24. Blumenfeld LC, Siatkowski RM, Johnson RA, Feuer WJ, Flynn JT. Retinopathy of prematurity in multiple-gestation pregnancies. *Am J Ophthalmol*. 1998;125(2):197–203.
25. Jain T. Socioeconomic and racial disparities among infertility patients seeking care. *Fertil Steril*. 2006;85(4):876–881.
26. Feinberg EC, Larsen FW, Catherino WH, Zhang J, Armstrong AY. Comparison of assisted reproductive technology utilization and outcomes between Caucasian and African American patients in an equal-access-to-care setting. *Fertil Steril*. 2006;85(4):888–894.
27. Seifer DB, Frazier LM, Grainger DA. Disparity in assisted reproductive technologies outcomes in black women compared with white women. *Fertil Steril*. 2008;90(5):1701–1710.
28. Zayed MA, Uppal A, Hartnett ME. New-onset maternal gestational hypertension and risk of genetic susceptibility to retinopathy of prematurity. *Invest Ophthalmol Vis Sci*. 2010;51(10):4983–4988.
29. Moll AC, Imhof SM, Cruysberg JR, Schouten-van Meeteren AY, Boers M, van Leeuwen FE. Incidence of retinoblastoma in children born after in-vitro fertilisation. *Lancet*. 2003;361(9354):309–310.
30. Amor DJ, Halliday J. A review of known imprinting syndromes and their association with assisted reproduction technologies. *Hum Reprod*. 2008;23(12):2826–2834.
31. Bizzaro MJ, Hussain N, Jonsson B, et al. Genetic susceptibility to retinopathy of prematurity. *Pediatrics*. 2006;118(5):1858–1863.