RBMO

REVIEW

Changes in visual function and ocular morphology in women who have undergone ART treatment and children born as a result of ART treatment: a systematic review

BIOGRAPHY

Stefano Palomba is Professor of Obstetrics and Gynaecology at Grande Ospedale Metropolitano of Reggio Calabria (Italy), and author of more than 220 peer-reviewed papers with a personal h-index of 36. His field of interest is reproductive medicine and surgery. He is the editor-in-chief and an editorial board member of several international journals.

Mario D. Toro[1], Michele Reibaldi[2], Antonio Longo[2], Teresio Avitabile[2], Maria E. Lionetti[3], Sarah Tripodi[2], Chiara Posarelli[4], Stefano Palomba[5,*]

KEY MESSAGE

Although sparse data suggest that assisted reproductive technology (ART) treatment can influence visual function and ocular morphology in women who have undergone ART treatment and children born as a result of ART treatment, the available evidence is inconclusive given its low level and quality.

ABSTRACT

As all the structures of the human eye are characterized by sex hormone receptors, this study tested the hypothesis that assisted reproductive technology (ART) treatment influences visual function and ocular morphology in women who have undergone ART treatment and children born as a result of ART treatment. A systematic literature search of all original articles published up to August 2018 was performed using the PubMed database, including all original studies available in the literature. Review articles, studies in which participants underwent mixed interventions (i.e. other than ART treatment), studies reporting data on ocular malformations in ART offspring, and studies written in languages other than English were excluded. All selected articles were analysed to assess the level of evidence according to the Oxford Centre for Evidence-Based Medicine 2011 guidelines, and the quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation system. Although sparse data suggest that ART treatment can influence visual function and ocular morphology in women who have undergone ART treatment and children born as a result of ART treatment, the available evidence is inconclusive given its low level and quality. More high-quality research is needed to assess the potential interaction between ART treatment and the eye.

[1] Department of General Ophthalmology, Medical University of Lublin, Poland
[2] Eye Clinic, University of Catania, Italy
[3] Department of Paediatrics, Marche Polytechnic University, Ancona, Italy
[4] Department of Surgical, Medical, Molecular Pathology and of Critical Area, University of Pisa, Pisa, Italy
[5] Department of Gynaecology and Obstetrics, Grande Ospedale Metropolitano of Reggio Calabria, Reggio Calabria, Italy

*Corresponding author. E-mail address: stefanopalomba@tin.it (S Palomba). https://doi.org/10.1016/j.rbmo.2018.11.007
1472-6483/
Declaration: The authors report no financial or commercial conflicts of interest.

KEYWORDS
ART
Eye
ICSI
IVF
Infertility
Sterility

INTRODUCTION

The eye is a target for sex hormones, as demonstrated by the presence of oestrogen, progesterone and androgen receptors in many specific ocular structures, such as the cornea, lens, iris, ciliary body, retina, lacrimal and meibomian glands, and conjunctiva (*Gupta et al., 2005; Nuzzi et al., 2018; Parihar et al., 2016*). Oestrogens, progestins and androgens are present in the tear film, aqueous humor, vitreous and retina, and are metabolized by the cornea, iris, ciliary body, lens and retina (*Wickham et al., 2000*).

Women who undergo assisted reproductive technology (ART) treatment are exposed to wide changes in sex hormone concentrations. For example, serum oestradiol levels can vary from deep hypo-oestrogenism, due to gonadotropin-releasing hormone agonist (GnRHa) or antagonist (GnRHant) Treatment, to hyperoestrogenism, due to gonadotropin controlled ovarian hyperstimulation (COH). Many studies suggest changes in ocular morphology and function during specific physiological conditions, such as postmenopause and pregnancy. Similarly, the relationship between sex hormones and the eye has also been studied in patients receiving oral contraception or hormone replacement therapy (HRT).

Sex hormones seem to control the differentiation process, gene expression and lipid production of glands (*Schneider and Paus, 2010*). Specifically, androgens increase lipid production by the meibomian gland (*Krenzer et al., 2000*), so androgen deficiency is a contributing factor to keratoconjunctivitis sicca ('dry eye') (*Sullivan et al., 2002*). Conversely, the impact of oestrogens on the eye is more uncertain. Contradictory findings exist regarding the effects of postmenopausal hypo-oestrogenism and HRT on ocular structures (*Gibson et al., 2017*). Postmenopausal women have a higher incidence of dry eye (*Peck et al., 2017*), but it is not known whether HRT increases or decreases the risk of dry eye because significant differences have been detected between oestrogen-only HRT and oestro-progestin HRT (*Ablamowicz et al., 2016*). Oestrogen administration improves the symptoms of dry eye, and exhibits a protective effect against glaucoma (*Abramov et al., 2005*), cataractogenesis and degradation of corneal collagen (*Aina et al., 2006*), and diabetic retinopathy (*Nixon and Simpkins, 2012*). On the other hand, neuro-ophthalmologic or vascular retinal complications (*Moschos and Nitoda, 2017*); reduced tear, lipid and mucus secretion; alterations in corneal thickness and biomechanics; and lens opacities are detected in women treated with oral contraceptives (*Spoerl et al., 2007; Tomlinson et al., 2001*).

The thickness and curvature of the cornea increase during pregnancy and return to basal parameters after delivery (*Goldich et al., 2014; Park et al., 1992*). These physiological changes can be due to fluid retention in the body during pregnancy (*Sen et al., 2013*), but can also be due to the activation of oestrogen, progesterone and androgen receptors in human corneal epithelial, stromal and endothelial cells (*Gupta et al., 2005*). Intraocular pressure (IOP) decreases during pregnancy, achieving the nadir during the third trimester and persisting for many months after delivery (*Vajaranant et al., 2016*). Even if an increased concentration of angiogenic factors could play a role (*Al-Gharbi et al., 2015; Rhee et al., 1999*), recent data demonstrate that oestrogens increase the uveoscleral outflow and decrease the episcleral venous pressure (*Dewundara et al., 2016*), playing a potential role in the pathogenesis of primary open angle glaucoma (*Salim, 2014*). Conversely, the role of progesterone in IOP is unclear. It could reduce IOP by antagonizing the effects of oestrogens, as observed in patients receiving medroxyprogesterone acetate (*Vajaranant et al., 2016*).

Based on these considerations, it could be hypothesized that changes in sex hormones related to ART treatment could affect the eyes of women who have undergone ART treatment and children born as a result of ART treatment. This systematic review aimed to analyse data available in the literature regarding changes in visual function and ocular morphology in women who have undergone ART treatment and children born as a result of ART treatment.

MATERIALS AND METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (*Moher et al., 2009*). The review protocol was not recorded at study design, and no registration number is available for consultation.

The methodology used for this comprehensive review consisted of a systematic search of all available articles exploring the effects of ART treatment on the eye (i.e. ocular function and morphology) in women who have undergone ART treatment and children born as a result of ART treatment. ART treatment was considered as all interventions for fertility enhancement, including gamete manipulation.

A literature search of all original articles published up to August 2018 was performed in parallel by two authors (ST and SP) using the PubMed database. The terms 'assisted conception', 'assisted reproductive technologies', 'intracytoplasmic sperm injection', 'intrauterine insemination', 'ICSI', 'in vitro fertilization', 'IVF' and 'ovarian stimulation' were searched in combination with 'birth eye defect', 'cornea', 'eye', 'intraocular pressure', 'neovascular membrane', 'ocular assessment', 'ocular surface', 'retina', 'retinal detachment', 'retinal vascular occlusion', 'retinoblastoma' and 'retinopathy'. Furthermore, the reference lists of all identified articles were examined manually to identify any potential studies that were not captured by the electronic searches.

After preparation of the list of all electronic data captured, two reviewers (ST and SP) examined the titles and abstracts independently and identified relevant articles. As no clear data on this issue were available in the literature at study design, in order to define a primary endpoint, all studies available in the literature reporting original data on visual function and ocular morphology in women who had undergone ART treatment and children born as a result of ART treatment were initially included in the analysis without restriction for study design, sample size and intervention performed. Exclusion criteria were: review studies, studies in which participants underwent mixed interventions (i.e. other than ART treatment), studies reporting data on ocular malformations in ART offspring, and studies written in languages other than English.

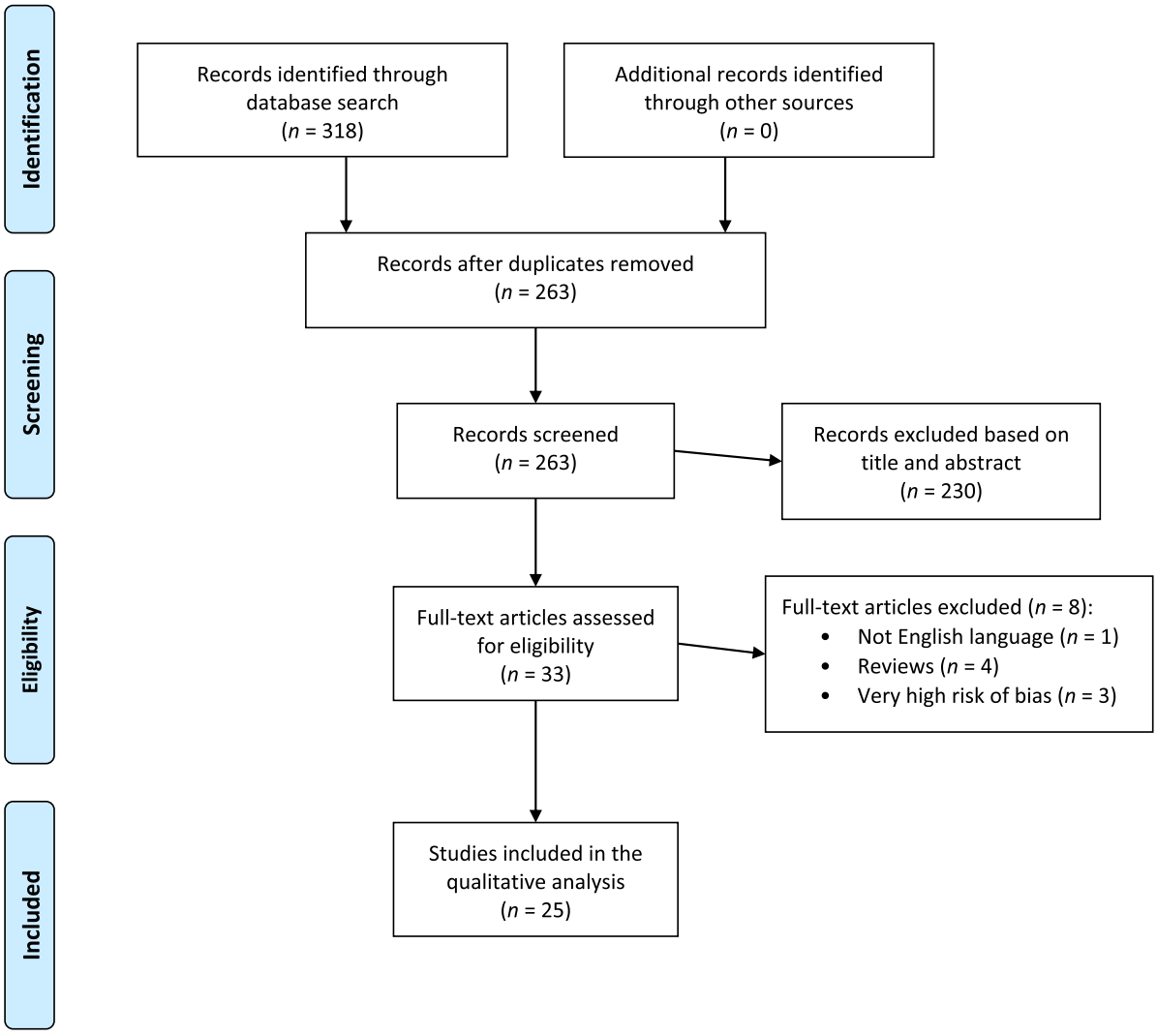

FIGURE 1 Flow diagram of the study according to PRISMA guidelines (*Moher et al., 2009*).

The same reviewers registered and selected the captured studies according to the inclusion and exclusion criteria by examining the full text of articles. Any disagreement was assessed by consensus, and a third reviewer (MDT) was consulted when necessary. Two reviewers independently extracted the following data using an Excel spreadsheet: study title, author, year of publication, study design, number of participants, type of ART employed, drugs and protocols used for COH, ocular changes, complications in ART women and ART offspring, and potential biases and/or confounders (i.e. other non-ART interventions, health status of women and children, outcome assessed in pregnant/non-pregnant patients, prematurity/low birth weight of newborns, etc.). No effort was made to contact the corresponding authors for further unpublished data.

All selected articles were analysed to assess the level of evidence according to the Oxford Centre for Evidence-Based Medicine (OCEM) 2011 guidelines (*Howick et al., 2010*), and the quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (*Guyatt et al., 2011*).

RESULTS

The results of the search strategy are summarized in FIGURE 1. From 318 articles extracted from the initial research, 263 abstracts were identified for screening and 25 of these met the inclusion/exclusion criteria for full-text review. Eight articles were excluded: one was not written in English, four were review papers, and three had severe bias (mixed interventions) (i.e. ocular changes due to hormonal pre-treatment rather than ART treatment in two articles, and retinopathy linked with very-low birth weight instead of ART treatment in one article) (FIGURE 1).

The characteristics of the 25 studies included in this systematic review were subgrouped considering ocular changes in women who had undergone ART treatment (TABLE 1) and children born as a result of ART treatment (TABLE 2). Specifically, seven studies evaluated the influence of ART treatment in women, and 18 articles studied ocular complications in ART offspring. Only one study was a prospective non-controlled trial; the other studies were prospective cohort studies (n=4), retrospective cohort studies (n=12), case reports/case series (n=7) and a cross-sectional study (n=1).

The following outcomes were assessed in women who had undergone ART treatment: changes in the ocular

surface and cornea, changes in IOP and development of glaucoma, onset of choroidal neovascularization (CNV), retinal detachment and vascular occlusion, development of ocular myasthenia gravis (OMG), diabetic retinopathy and macular degeneration. Visual acuity and refractive errors, retinal vascular status and presence of retinopathy of prematurity (ROP), incidence of retinoblastoma and ocular complications were studied in children born as a result of ART treatment.

TABLE 3 summarizes the level and quality of the available evidence about the effects of ART treatment on the eye in women who had undergone ART treatment and children born as a result of ART treatment according to the OCEM guidelines (*Howick et al., 2010*) and the GRADE system (*Guyatt et al., 2011*), respectively.

No data synthesis was possible for the heterogeneity of available data and the design of the available studies (i.e. case reports or case series). Thus, the current systematic review reports a qualitative analysis, detailed issue-by-issue below in narrative fashion.

Ocular changes in women following ART treatment

Ocular surface

The lacrimal function unit is composed of ocular surface epithelia, lacrimal glands, other minor lacrimal glands, and innervation that regulates the tear film and its secretion. Damage of one of these components leads to dry eye symptoms (*Stern et al., 2004*).

A prospective non-controlled study on 117 patients showed that women who had undergone ART treatment developed dry eye symptoms, assessed using the Schirmer test (test aimed to measure tear secretion). At baseline, 10 of 32 patients reported Schirmer values <10 mm in at least one eye. Moreover, no increase in the number of patients with dry eye was detected after treatment (assessed during the first trimester of pregnancy) (*Parihar et al., 2016*).

TABLE 1 OCULAR CHANGES IN WOMEN WHO UNDERWENT ASSISTED REPRODUCTIVE TECHNOLOGY (ART) TREATMENT

Author	Year	Country	Study design	Sample (*n*)	Age (years, mean ± SD)	Follow-up (months)	ART (type)	ART treatment (*n*)	Protocol/ drug(s)	Pregnancy (*n*)	Ocular assessment (timing)	Ocular changes
Ciucci	2015	Italy	CR	1	31	4	IVF	NR	GnRHa (buserelin 0.2 ml twice daily for 10 days and then 0.5 ml twice daily for 9 days), rFSH (follitropin α, 350 IU/day for 10 days) and progesterone (100 mg/day for 3 days)	0	7 days after rFSH	CNV onset
Dolz-Marco	2017	NR	CS	3	30	5–12	IVF	Cases 1 and 2: 1. Case 3: 4	Case 1: GnRHa (triptorelin), menotropin and rFSH (follitropin α); Case 2: GnRH antagonist (cetrorelix), rFSH (follitropin α) and GnRHa (triptorelin); Case 3: uFSH and hCG	NR	Case 1: last 15 days of treatment; Case 2: last 12 days of treatment; Case 3: fourth hormonal treatment cycle	CNV onset
Lee	2010	NR	CR	1	30	6	IVF	NR	GnRH antagonist (cetrorelix 3 mg/day for 4 days) and rFSH (follitropin α, 225 IU/day for 10 days)	NR	10 days after GnRH antagonist administration	Retinal vascular occlusion

(continued on next page)

Table 1 – (continued)

Author	Year	Country	Study design	Sample (*n*)	Age (years, mean ± SD)	Follow-up (months)	ART (type)	ART treatment (*n*)	Protocol/ drug(s)	Pregnancy (*n*)	Ocular assessment (timing)	Ocular changes
Parihar	2016	India	PU	32	27 ± 1.14	12	IVF	1 for 54 patients and 2 for 46 patients	Oral contraceptive and GnRHa injection	32 patients followed up to third trimester of pregnancy	Beginning of menstrual cycle at day zero (baseline), at day 21 (post-oral contraceptives), at the time of induction (post-GnRHa injection), on conception (first trimester), during the third trimester and at 3 months post-delivery	No change in lacrimal function, corneal thickness, endothelial cell count and IOP
Ratson	2016	Israel	RC	4364 versus 101,640[a]	30.4 ± 5.6 versus 28.4 ± 5.9[a]	26 years	IVF/OI	NR	NR	106,004	NR	Retinal detachment onset
Yoo	2018	Korea	CR	1	37	12	IVF	1	Intramuscular progesterone injection (200 mg/day)	0	1 day after treatment	Ocular myasthenia gravis exacerbation
Yuksel	2016	Turkey	CS	3	32.3 ± 3.6	15.6 ± 3.2	IVF	Case 1: 2; Case 2: 4; Case 3: 2	Case 1: GnRHa, hCG and IP; Case 2: CC + rFSH, hCG and IP; Case 3: rFSH, hCG and IP	0	NR	Keratoconus progression

CC, clomiphene citrate; CNV, choroidal neovascularization; CR, case report; CS, case series; GnRHa, gonadotropin-releasing hormone agonist; hCG, human chorionic gonadotropin; IOP, intraocular pressure; IVF, in-vitro fertilization; IP, intravaginal progesterone; NR, not reported; OI, ovulation induction; PU, prospective uncontrolled; RC, retrospective cohort; rFSH, recombinant follicle-stimulating hormone; SD, standard deviation; uFSH, urinary follicle-stimulating hormone.

[a] Experimental versus control group.

Cornea

The cornea is an avascular and transparent tissue with refractive and barrier functions to fluid and pathogens. It is supported by basement membrane and Bowman's layer. The stroma composes the majority of the corneal volume, provides support and clarity, and assists in ocular immunity. The posterior cornea, composed of Descemet membrane and endothelium, is essential for stromal dehydration (*Eghrari et al., 2015*).

In 2016, a prospective uncontrolled study (*Parihar et al., 2016*) demonstrated a non-significant change in corneal thickness [mean ± standard deviation (SD)] during the first trimester of pregnancy after ART treatment (503.34 ± 1.04 μm and 503.32 ± 1.27 μm for the right and left eyes, respectively) in comparison with baseline (501.07 ± 1.21 μm and 501.30 ± 1.68 μm for the right and left eyes, respectively). Similarly, the corneal endothelial cell count (mean ± SD) showed a non-significant increase during the first trimester of pregnancy after ART treatment (3015.12 ± 14.23 cells per mm^2 and 3014.23 ± 14.20 cells per mm^2 for the right and left eyes, respectively) compared with baseline (3010.30 ± 12.72 cells per mm^2 and 3012.90 ± 12.99 cells per mm^2 for the right and left eyes, respectively) (*Parihar et al., 2016*).

A case series study (*Yuksel et al., 2016*) of three women with keratoconus showed progression of the disease in both eyes following in-vitro fertilization (IVF) treatment. Two women complained of decreased vision 2 months after the second IVF treatment, and the other woman reported visual problems 1 month after the third IVF treatment. The patients used different COH protocols (TABLE 1). During follow-up, four eyes of the three patients underwent corneal

TABLE 2 OCULAR CHANGES IN OFFSPRING BORN AS A RESULT OF ASSISTED REPRODUCTIVE TECHNOLOGY (ART) TREATMENT

Author	Year	Country	Study design	Sample (*n*)	Age at diagnosis	Follow-up (years)	Type of ART treatment	Treatments performed	Ocular assessments
Anteby	2001	Israel	PU	47	2 months–5 years	5	IVF/ICSI	NR	Poor visual acuity and hyperopia, RB and ROP onset (two cases)
Axer-Siegel	2005	Israel	PC	62 versus 71[a]	Birth	1	IVF	NR	No effect on biometric and keratometric values, nor on IOP in premature children. ROP onset
Axer-Siegel	2007	Israel	PC	32 versus 34[a]	Birth	6 months	IVF	NR	No biometric and IOP value changes, smaller keratometric values, higher pachymetric values and retinal haemorrhages
Barker	2017	UK	RC	81 versus 124[a]	Birth	4	IVF[b]/ICSI/ clomiphene	NR	No effect on ROP onset but higher proportion of babies requiring treatment in multiple pregnancies
Bradbury	2004	UK	RC	358,270	Birth–5 years	12	IVF	NR	RB onset
Cruysberg	2002	Netherlands	CR	1	3 years	10 months	IVF	NR	Bilateral RB
Foix-L'Helias	2012	France	RC	28,170	Birth–5 years	6	Every	NR	RB onset
Funnel	2007	UK	RC	790	Birth	3	IVF/ICSI	NR	ROP onset
Jafarzade-hpur	2013	Iran	CrS	320	3 and 9 months	9 months	IVF/ICSI	NR	Hyperopia and poor fixation
Kallen	2010	Sweden	RC	26,692	NR	23	IVF	NR	RB onset
Lideegard	2005	Denmark	RC	442,349 versus 6052[a]	NR	4.5	IVF	NR	RB onset
Marees	2009	Netherlands	RC	40,330	8.5–38 months	7	IVF	From one to eight cycles of IVF	RB onset
Mckibbin	1996	UK	RC	44 versus 267[a]	Birth	3	IVF/ICSI/IUI[b]	NR	ROP onset
Moll	2003	Netherlands	CS	5	8.5–38 months	2	IVF/ICSI	From one to eight cycles of IVF	RB onset
Tornqvist	2010	Sweden	RC	31,850	NR	25	IVF/ICSI	NR	No effect on visual acuity after adjusting data. ROP onset (one case)
Watts	2000	UK	RC	21 versus 179[a]	Birth	3	IVF/ICSI/IUI/ clomiphene	NR	ROP onset
Wikstrand	2006	Sweden	RC	137 versus 159[a]	5 years	2	ICSI	NR	No effect on visual acuity and refractive errors. ROP onset (one case)
Wikstrand	2008	Sweden	PC	82 versus 181[a]	Between 4.9 and 6 years in the ART group and between 3 and 19 years in the control group	NR	ICSI	NR	Abnormal retinal vascularization with lower vascular branching points

CR, case report; CS, case series; CrS, cross-sectional; ICSI, intracytoplasmic sperm injection; IOP, intraocular pressure; IUI, intrauterine insemination; IVF, in-vitro fertilization; NR, not reported; PC, prospective controlled study; PU, prospective uncontrolled study; RB, retinoblastoma; RC, retrospective cohort study; ROP, retinopathy of prematurity.

[a] Patients versus controls.

[b] Including cycles with embryo, oocyte and sperm donation.

TABLE 3 BEST EVIDENCE LEVEL AND QUALITY FOR THE MAIN OUTCOMES ASSESSED IN WOMEN WHO HAD UNDERGONE ASSISTED REPRODUCTIVE TECHNOLOGY (ART) TREATMENT AND CHILDREN BORN AS A RESULT OF ART TREATMENT

		Evidence		
	Outcome	**Level**[a]	**Quality**[b]	**Reference**
Women who had undergone ART treatment	CNV	4	Very low	*Ciucci et al., 2015*
	CNV	4	Very low	*Dolz-Marco et al., 2017*
	RVO	4	Very low	*Lee et al., 2010*
	Change in corneal thickness and cellularity	3	Very low	*Parihar et al., 2016*
	Retinal detachment	3	Very low	*Ratson et al., 2016*
	Increased IOP/glaucoma	3	Very low	*Parihar et al., 2016; Ratson et al., 2016*
	Diabetic retinopathy	3	Very low	*Ratson et al., 2016*
	Macular degeneration	3	Very low	*Ratson et al., 2016*
	OMG	4	Very low	*Yoo et al., 2018*
	Keratoconus progression	4	Very low	*Yuksel et al., 2016*
Children born as a result of ART treatment	Hyperopia, RB and ROP	3	Low	*Anteby et al., 2001*
	Biometric and keratometric values, IOP and retinal vascular status[c]	3	Low	*Axer-Siegel et al., 2005*
	IOP, keratometry, biometry, pachymetry and retinal vascular status	3	Low	*Axer-Siegel et al., 2007*
	ROP	3	Low	*Barker et al., 2017*
	RB	3	Low	*Bradbury et al., 2004*
	RB	4	Very low	*Cruysberg et al., 2002*
	RB	3	Low	*Foix-L'helias et al., 2012*
	ROP	3	Low	*Funnel and Dabb, 2007*
	Hyperopia	3	Low	*Jafarzadehpur et al., 2013*
	RB	3	Low	*Kallen et al., 2010*
	RB	3	Low	*Lideegard et al., 2005*
	RB	3	Very low	*Marees et al., 2009*
	ROP	3	Low	*McKibbin and Dabbs, 1996*
	RB	4	Very low	*Moll et al., 2003*
	Visual acuity	3	Low	*Tornqvist et al., 2010*
	ROP	3	Low	*Watts and Adams, 2000*
	Refractive errors and ROP	3	Low	*Wikstrand et al., 2006*
	Retinal vascular status	3	Low	*Wikstrand et al., 2008*

CNV, choroidal neovascularization; IOP, intraocular pressure; OMG, ocular myasthenia gravis; RB, retinoblastoma; ROP, retinopathy of prematurity; RVO, retinal vein occlusion.

[a] Assessed following the Oxford Centre for Evidence-Based Medicine Levels of Evidence 2011 guidelines (*Howick et al., 2010*).

[b] Assessed using the Grading of Recommendations Assessment, Development and Evaluation system (*Guyatt et al., 2011*).

[c] Outcomes referred to premature infants.

cross-linking, and no progression was detected after this treatment (*Yuksel et al., 2016*).

Intraocular pressure

Increased IOP is the primary risk factor for development and progression of glaucoma. An increase in IOP damages the optic nerve and ganglion cells, whereas a reduction in IOP can slow/prevent the progression of glaucoma. Currently, lowering IOP is the only therapy available to treat glaucoma (*Sihota et al., 2018*).

A population-based retrospective cohort study (*Ratson et al., 2016*), conducted on 106,004 women with no history of ophthalmic diseases who delivered between 1988 and 2013, demonstrated a non-significant risk (0% versus 0.003%, P=0.514) of developing glaucoma in women who received fertility treatment (n=4364) in comparison with women who did not receive fertility treatment (n=101,640).

Parihar et al. (2016) found no significant change in IOP (mean ± SD) during the first trimester of pregnancy following ART treatment (13.02 ± 1.23 mmHg and 13.21 ± 1.20 mmHg for the right and left eyes, respectively) compared with baseline (13.94 ± 1.71 mmHg and 13.93 ± 1.75 mmHg for the right and left eyes, respectively).

Choroidal neovascularization

CNV is a common cause of blindness in developed countries, and is due to an imbalance between factors that inhibit and enhance angiogenesis (*Spaide, 1999*). It is mainly associated with other ocular conditions such as age-related macular degeneration, myopia, or inflammatory or hereditary retinal diseases. When CNV occurs in patients aged <50 years without any primary ocular or systemic diseases, it is classified as idiopathic CNV (*Cohen et al., 1996*).

Only two case series studies on CNV and ART treatment have been published (*Ciucci et al., 2015; Dolz-Marco et al., 2017*). *Ciucci et al. (2015)* described the case of a 31-year-old woman who presented with a sudden decrease and distorted vision in her right eye. She had received medications for IVF in the preceding weeks (TABLE 1). The patient reported onset of visual symptoms 7 days after treatment with follitropin α. The diagnosis of idiopathic CNV was confirmed by optical coherence tomography (OCT), and both fluorescein and green angiography. The woman decided to interrupt COH and cancel the IVF cycle. She was treated successfully with three consecutive monthly intravitreal injections of bevacizumab, and visual acuity was restored with regression of CNV (*Ciucci et al., 2015*). *Dolz-Marco et al. (2017)* reported three women who developed unilateral acuity vision loss and metamorphopsia. Fundus examination and OCT demonstrated the presence of CNV. All patients were undergoing COH with different gonadotropins following GnRHa down-regulation (TABLE 1). Intravitreal therapy with ranibizumab resulted in a significant functional and anatomical improvement in all three women (*Dolz-Marco et al., 2017*).

Exudative retinal detachment

Exudative retinal detachment (ERD) occurs when fluid collects in the subretinal space between the photoreceptors and the retinal pigment epithelium. In the developed eye, this space is minimal, although it can be re-opened by pathological conditions that disrupt the integrity of the blood–retinal barrier, such as inflammatory, infectious, infiltrative, neoplastic, vascular and degenerative conditions. This can lead to ERD (*Amer et al., 2017*).

Ratson et al. (2016) reported a significantly higher risk of developing ERD in patients who had undergone IVF in comparison with patients who received ovulation induction and healthy women without a history of fertility treatment (0.3% versus 0.1% versus 0.1% for the three study groups, respectively). IVF was found to be an independent risk factor for developing ERD even after removing confounders such as maternal age, obesity and parity [adjusted hazard risk 3.4, 95% coefficient interval (CI) 1.2–9.3] (*Ratson et al., 2016*).

Retinal vein occlusion

Retinal vein occlusion (RVO) is one of the most common causes of a retinal vascular abnormality and a frequent cause of visual loss. It is characterized by engorgement and dilatation of the retinal veins due to increased retinal venous blood pressure causing haemorrhage, and several degrees of retinal ischaemia and oedema. When RVO occurs in the foveal region, it can cause loss of vision (*Jonas et al., 2017*).

Only one case report (*Lee et al., 2010*) has been published on the relationship between RVO and ART treatment. A 30-year-old woman presented with decreased visual acuity in the left eye for 2 weeks. Fundus examination in the left eye showed moderate tortuosity of both temporal vascular arcades, and dilation of the inferior temporal vein with a haemorrhage (*Lee et al., 2010*). The supero-temporal macular area was swollen and pale. On fluorescein angiogram, there was moderate leakage from the involved vessels in the late phase. The patient was diagnosed with incomplete non-ischaemic central RVO followed by branch retinal artery occlusion, observed 10 days after GnRHa administration for IVF (TABLE 1). Six months later, the patient recovered her sight without any treatment (*Lee et al., 2010*).

Ocular myasthenia gravis

Myasthenia gravis is an autoimmune disease that affects the neuromuscular junction, resulting in symptoms of muscle weakness and fatigability (*Nair et al., 2014*). OMG is a form of myasthenia gravis in which weakness is restricted to the ocular muscles and may produce significant visual disability. Patients present with fluctuating ptosis, diplopia or both (*Al-Haidar et al., 2018*).

Only one case report (*Yoo et al., 2018*) of OMG, occurring in a 37-year-old woman the day after her first IVF procedure, is available in the literature. She experienced sudden intermittent binocular horizontal diplopia (which improved after rest and worsened in the afternoon), intermittent exotropia and bilateral ptosis (worsening after fatigue). She was prescribed with pyridostigmine bromide, and the ocular deviation and bilateral ptosis improved 2 weeks after starting treatment. No evidence of conversion to generalized myasthenia gravis was detected during 1 year of follow-up (*Yoo et al., 2018*).

Other ophthalmic complications

The population-based study by *Ratson et al. (2016)* demonstrated a non-significant difference between patients who underwent IVF and patients who received ovulation induction and healthy women without a history of fertility treatment in terms of diabetic retinopathy (0.01% versus 0.01% versus 0.05% for the three study groups, respectively, P=0.793) and macular degeneration (0% versus 0% versus 0.05% for the three study groups, respectively, P=0.807).

Ocular issues in children born as a result of ART treatment

ART pregnancies are associated with several fetal/neonatal risks, including prematurity and low birth weight, congenital malformations and imprinting disorders (*Palomba et al., 2016a,b*). In the literature, the potential effects of ART treatment on the eyes of offspring are limited to three main fields of interest: visual function and ocular malformations, ROP and retinoblastoma. The risk of ocular malformations in women who had undergone ART treatment was not covered in this review as many recent systematic reviews are already available in the literature.

Visual function

In 2001, the first study on visual function in ART offspring was published on 47 babies (25 girls and 22 boys) conceived by IVF between July 1994 and December 1995, and examined in a paediatric ophthalmology unit in Israel (*Anteby et al., 2001*). At the time of examination, among 70 eyes of 35 non-verbal children, six (9%) had poor or abnormal vision. Among 12 verbal children, visual acuity was poor in seven eyes. Cyclopegic refraction was possible in 82 eyes because of pathological conditions, and showed hypermetropic refraction >1 D in 47 eyes (57%),

refractive error >3 D in 20 eyes and anysometropia >1 D in eight children. Moreover, in 43 IVF children, ocular motility and cover tests showed that 31 babies were orthophoric (72%), seven (16%) were esotropic and five (12%) were exotropic (*Anteby et al., 2001*).

Subsequently, a cohort study (*Axer-Siegel et al., 2005*), conducted in the Neonatal Intensive Care Unit of Israel from June 2003 to June 2004, evaluated ocular biometry, corneal curvature, IOP and retinal vascularization in 133 premature infants born following IVF (62/133, 46.6%) and compared the results with infants born following natural conception (71/133, 53.4%). The IVF and natural conception groups were not significantly different in terms of gestational age, birth weight, neonatal biometry, APGAR score and rate of twin pregnancies (*Axer-Siegel et al., 2005*). No significant differences linked with the conception method were found for biometric, keratometric and IOP data. Data analysis according to postconceptional age (PCA) at examination revealed a significant relationship between PCA and axial lengths of the right and left eyes (R=0.686 and R=0.675, respectively), and horizontal and vertical corneal radius of curvature (horizontal: R=0.489 and R=0.346 for the right and left eyes, respectively; vertical: R=0.327 and R=0.356 for the right and left eyes, respectively) irrespective of the conception method (*Axer-Siegel et al., 2005*).

A case–control matched study (*Wikstrand et al., 2006*) investigated visual function and ocular morphology in 137 children (67 boys and 70 girls) born following intracytoplasmic sperm injection (ICSI), and compared the results with 159 children (77 boys and 82 girls) born following natural conception in Sweden between 1994 and 1996. Although the ICSI group included 38 twins (27.7% versus 1.3% for the natural conception group), no significant differences in refractive errors [odds ratio (OR) 1.3%, 95% CI 0.4–4.1] and visual acuity (OR 0.6, 95% CI 0.2–1.6 for visual acuity of the best eye; OR 0.8, 95% CI 0.1–6.9 for intereye difference in visual acuity) were found between the ICSI and natural conception groups (*Wikstrand et al., 2006*). In addition, the measurements of palpebral fissure length in the right and left eyes were not significantly different between the groups (*Wikstrand et al., 2006*).

In 2007, a case–control study (*Axer-Siegel et al., 2007*) was performed on 66 full-term infants (32 IVF infants and 34 naturally conceived infants) at 1 year of age at Rabin Medical Center, Israel. The mean horizontal and vertical corneal curvatures (R1/R2) were significantly smaller in the IVF group (R1=6.99 mm and R2=6.63 mm for the right and left eyes, respectively) compared with the natural conception group (R1=7.20 mm and 7.18 mm for the right and left eyes, respectively; R2=6.80 mm for the right and left eyes). After controlling data for birth weight and body length, the difference remained significant only for babies with birth weight <3000 g and body length <48.5 cm (*Axer-Siegel et al., 2007*). Pachymetric values were higher in the IVF group (579.8 µm and 579.5 µm for the right and left eyes, respectively) than the natural conception group (559.3 µm and 552.7 µm for the right and left eyes, respectively) (*Axer-Siegel et al., 2007*). Moreover, the differences were not significant for the right eyes yet were significant for the left eyes (P=0.047) (*Axer-Siegel et al., 2007*). No significant differences in axial length, anterior chamber depth, lens thickness and IOP were found between the groups.

A large observational cohort study (*Tornqvist et al., 2010*) was conducted on visual impairment in 24,628 IVF children born from 1985 to 2005 in Sweden, with all children born during the corresponding years used as the control group. Increased incidence of severe visual impairment [adjusted OR (aOR) 1.55, 95% CI 1.04–2.32] was detected after adjusting the data for various confounders (year of birth, maternal age, parity, smoking, body mass index, etc.). Moreover, more than half of the children were born prematurely (13/25, 52%), and when these children were excluded from the data analysis, the aOR showed no significant difference (aOR 1.41, 95% CI 0.81–2.45) between the groups. Of note, 11 of the 25 IVF children with visual impairment (44%) were twins (*Tornqvist et al., 2010*).

More recently, a cross-sectional cohort study (*Jafarzadehpur et al., 2013*) conducted in Iran on 320 infants born following IVF or ICSI procedures confirmed that 20.3% of the infants had poor fixation and 2.9% showed manifest strabismus (Hirscgberg test). The results also revealed the presence of myopia, hyperopia and emmetropia in 2.9%, 87% and 10.1% of cases, respectively. These findings did not show any significant difference between the sexes. Fixation deficiency was significantly more common in preterm infants than in term infants [101/320 (18.8%) versus 219/320 (1.5%)], suggesting that fixation deficiency is closely related to prematurity (*Jafarzadehpur et al., 2013*). A significant correlation was found between refractive error and poor fixation, so failure of fixation control was observed more frequently with increasing refractive error (*Jafarzadehpur et al., 2013*).

Retinopathy of prematurity

ROP is a vasoproliferative retinal disorder and the most common preventable cause of childhood blindness worldwide. Its incidence is inversely proportional to gestational age and birth weight (*Quimson, 2015*).

In 1996, a retrospective study (*McKibbin and Dabbs, 1996*) investigated the relationship between ART babies and ROP for the first time. The authors reviewed the UK records of 16,208 babies born between August 1991 and December 1994, and those of 267 babies screened for ROP in the same period. Assisted conception accounted for 44 of the screened patients; 10 (22.7%) of these patients had ROP (any stage) and three had stage 3 ROP (two of whom required treatment for threshold disease). However, no significant difference was found in the incidence of ROP between babies conceived using ART or naturally (22.7% versus 29.6%, respectively) (*McKibbin and Dabbs, 1996*).

A retrospective study (*Watts and Adams, 2000*) re-examined the risk of developing stage 3 ROP in children born following ART treatment between 1995 and 1998, and its severity according to the different ART types. Among 179 babies, acute ROP was detected in 32.4% and stage 3 ROP developed in 15.6%. In total, 21 screened children (11.7%) were born following ART treatment: seven following IVF, five following ICSI, eight following clomiphene administration and one following intrauterine insemination (IUI). Seven babies (five conceived through IVF) were twins (15.9%) and reached stage 3 ROP. Of the babies who required treatment for ROP, 28.6% were born following ART treatment (83.3% after IVF) (*Watts and Adams, 2000*).

In 2001, a prospective controlled study (*Anteby et al., 2001*) on 47 babies born following IVF in Israel highlighted the onset of ROP in two children. One child reached stage 2 ROP in both eyes which regressed spontaneously, and the other child, one of a set of triplets, developed stage 5 ROP which required treatment (*Anteby et al., 2001*). Another case of ROP was detected in a child born following ICSI (*Wikstrand et al., 2006*). A cohort study (*Axer-Siegel et al., 2005*) observed 133 premature babies in Israel (71 born following natural conception and 62 born following IVF) and evaluated the retinal vascular status. Retinal vascularization was similar in all babies (53.2% and 45% in the IVF and natural conception groups, respectively). Stage 1 ROP was more prevalent in the natural conception group than the IVF group (2.8% versus 1.6%, respectively), whereas stage 2 ROP was more prevalent in the IVF group (6.5% versus 0%, respectively). However, the differences were not significant. The zone of retinal vascularization correlated with axial length and PCA in both groups, and it is known that retinal vascularization matures with elongation of the eye (*Axer-Siegel et al., 2005*). A case–control study (*Axer-Siegel et al., 2007*) investigated the retinal vascular status in 66 full-term babies (32 born following IVF and 34 following natural conception) in Israel in 2006, and retinal haemorrhages were found in six eyes of three infants in the IVF group, and in five eyes of three infants in the natural conception group; retinal vascularization was normal in all infants (*Axer-Siegel et al., 2007*). Finally, a retrospective study (*Funnell and Dabbs, 2007*) investigated infants screened for ROP in the UK between April 2000 and August 2003. During the study period, 12,737 naturally conceived babies and 790 ART babies were studied, and 248 babies were screened for ROP. Specifically, 1.6% of naturally conceived babies required ROP screening compared with 4.2% of babies born following ART treatment. The incidence of ROP screening was two-fold lower (4.3%) among ART children than has been observed previously (20.3%) (*McKibbin and Dabbs, 1996*); this difference was significant.

Another cohort study (*Wikstrand et al., 2008*) investigated the ocular fundus morphology by digital image analysis of 82 children (67 boys and 70 girls) born following ICSI compared with 181 children who were conceived naturally (83 boys and 98 girls) between 1994 and 1996. Abnormal retinal vascularization was observed in the ICSI group, and the median number of vascular branching points was significantly lower compared with the natural conception group [25 (range 19–35), 95% CI 24.56–26.23 versus 27 (range 19–40), 95% CI 26.88–27.96, for the ICSI and natural conception groups, respectively] (*Wikstrand et al., 2008*). In addition, gender influenced the results significantly. In fact, the median number of branching points was significantly lower in boys compared with girls [24 (range 19–29.5) versus 26.5 (range 21–35), respectively]. No difference in the median number of branching points was found between girls in the ICSI group and girls in the natural conception group, whereas boys in the ICSI group had fewer branching points than boys in the natural conception group. Moreover, in the ICSI group, the children with lower birth weight had a tendency for a decrease in the number of retinal branching points, although this was not significant. Of note, close correlation was demonstrated between the number of branching points and the tortuosity index for arteries (r=−0.27) and veins (r=−0.26) in the ICSI group alone. However, no significant differences were noted for the optic disc and cup area, neuroretinal rim area, and arterial and venous tortuosity index between the ICSI and natural conception groups (*Wikstrand et al., 2008*).

More recently, *Barker et al. (2017)* analysed the risk of ROP in ART and non-ART children born as multiple pregnancies. In total, 24,229 live births were analysed, including 1015 babies from multiple pregnancies. Overall, 1272 babies met the ROP screening criteria, and 205 of these were multiple births (20.2% versus 4.6% of singleton babies). Among the 205 babies born as multiple births, 81 (39.5%) were born following ART treatment: 69 following IVF, two following ICSI and nine following clomiphene administration. No significant difference was observed between the number of babies developing ROP (34% versus 30.5% in the ART and non-ART groups, respectively; aOR 1.23, 95% CI 0.49–3.04). The proportion of babies who required treatment for ROP was slightly higher in ART babies than in non-ART babies (10% versus 8.5%, respectively) (*Barker et al., 2017*).

Retinoblastoma

Retinoblastoma is the most common tumour in children. Many cases are sporadic, albeit a small proportion of cases have a family history. The major risk factors are older maternal age, infections and environmental factors (*Moll et al., 2003*).

Anteby et al. (2001) reported a case of retinoblastoma in a study on 47 children born following ART treatment between 1994 and 1999 in Israel. A case of sporadic bilateral retinoblastoma in a 3-year-old girl born following IVF was reported in 2002 in the Netherlands (*Cruysberg et al., 2002*). External examination showed exotropia of the left eye, but on ophthalmic examination, a small retinoblastoma was found in the nasal periphery of the right eye, and a large retinoblastoma was found in the posterior pole of the left eye. The left eye was enucleated, and the right eye was treated by ruthenium plaque. An *RB1* gene mutation was seen during DNA analysis (*Cruysberg et al., 2002*).

A study (*Moll et al., 2003*) on the population-based retinoblastoma Dutch registry found an increased risk of retinoblastoma (relative risk 4.9, 95% CI 1.6–11.3) among children born following IVF between 1995 and 2001. Retinoblastoma was diagnosed in five patients born following IVF between 2001 and 2002. To calculate the relative risk of the disease, they assumed that the proportion of IVF children in the Netherlands was between 1% and 1.5% between 1995 and 2001, and that the five patients represented all new cases in the Netherlands during that period (*Moll et al., 2003*). More recently, another population-based study (*Marees et al., 2009*) in the Netherlands described a significantly increased risk (relative risk 2.5, 95% CI 1.0–5.2) of retinoblastoma in IVF children in the 1995–2007 period. From nationwide estimates of numbers of live births conceived by IVF (n=40,330), the authors estimated the expected numbers of patients with retinoblastoma in the period 1995–2007. The observed number of retinoblastoma cases was obtained by questionnaires sent to the parents of children with retinoblastoma diagnosed between 1995 and 2005. The Dutch retinoblastoma register contained a total of 162 eligible patients with retinoblastoma diagnosed between 1995 and 2007; that analysis demonstrated no significantly elevated risk (relative risk

1.29, 95% CI 0.16–4.66) in IVF children (*Marees et al., 2009*). A retrospective study (*Källén et al., 2010*) on 26,692 IVF children born between 1982 and 2005 in Sweden detected 53 cases of tumours, including two cases of retinoblastoma . After adjustment for year of birth, the risk for childhood cancer among IVF offspring was higher (aOR 1.4, 95% CI 1.09–1.87).

On the contrary, in the UK and Denmark, two population-based studies showed no increased risk of retinoblastoma among children born following IVF (*Bradbury and Jick, 2004; Lidegaard et al., 2005*). In the first study (*Bradbury and Jick, 2004*), the authors identified 358,270 live births occurring between 1989 and 2001, among which were 24 cases of retinoblastoma. Based on these data, they estimated a frequency of 6.7 cases of retinoblastoma per 100,000 births (95% CI 4.5–10) or one in 15,000 births. Over the follow-up period, the frequency of retinoblastoma cases increased from 3.9 per 100,000 live births (1989–1992) to 11.5 per 100,000 live births (1997–2001). For the same period, 1398 women had 2091 IVF attempts with a live birth in 8.4% of attempts. None of the 24 children with retinoblastoma were born following IVF (*Bradbury and Jick, 2004*). The second study (*Lidegaard et al., 2005*) analysed 442,349 non-IVF and 6052 IVF singleton children born in a 7-year study period (1995–2001). Five cases of retinoblastoma were observed in the cohort of non-IVF children, and no cases were detected in the IVF group (*Lidegaard et al., 2005*). Similarly, a retrospective study (*Foix-L'Helias et al., 2012*) conducted in France between 2000 and 2006 on 244 retinoblastoma cases showed no significant increased risk of retinoblastoma following infertility treatment, regardless of the type of treatment. In particular, the incidence of retinoblastoma was no higher in infertile patients who underwent both IVF/ICSI (aOR 1.4, 95% CI 0.6–2.9) and IUI/ovarian stimulation (aOR 1.3, 95% CI 0.8–2.4) compared with women who did not undergo fertility treatment (*Foix-L'Helias et al., 2012*). Moreover, the risk of retinoblastoma was two-fold higher in infertile patients (time to pregnancy >24 months) than in healthy patients (aOR 2.0, 95% CI 1.2–3.5) (*Foix-L'Helias et al., 2012*). The risk of retinoblastoma was not associated with paternal age, but increased with maternal age (*Foix-L'Helias et al., 2012*).

DISCUSSION

To the authors' knowledge, this is the first systematic review to investigate ocular changes in women who have undergone ART treatment and children born as a result of ART treatment.

Available data show that ART treatment did not significantly influence lacrimal function (*Parihar et al., 2016*), cornea thickness and cellularity (*Parihar et al., 2016*), and IOP (*Parihar et al., 2016*; *Ratson et al., 2016*). In addition, the risk of diabetic retinopathy and macular degeneration was not increased (*Ratson et al., 2016*). Cases of idiopathic CNV (*Ciucci et al., 2015; Dolz-Marco et al., 2017*), worsening of pre-existing keratoconus (*Yuksel et al., 2016*), non-ischaemic central RVO (*Lee et al., 2010*) and OMG (*Yoo et al., 2018*) were reported in patients who had undergone ART treatment. However, the risk was not clinically significant because the available data related to just four patients with idiopathic CNV (*Ciucci et al., 2015; Dolz-Marco et al., 2017*), three patients with worsening of keratoconus (*Yuksel et al., 2016*), and two patients with non-ischaemic central RVO (*Lee et al., 2010*) and OMG (*Yoo et al., 2018*). These clinical ophthalmic complications could be considered incidental given the number of patients who received ART treatment worldwide. In addition, <0.3% of ART patients had ERD (*Ratson et al., 2016*).

Current findings on the effects of ART treatment on the eyes of children born as a result of such treatment suggest that refractive and ocular motility disorders are more common in these children (*Anteby et al., 2001, Jafarzadehpur et al., 2013*), and that ART treatment reduces keratometric values and increases pachymetric values in children (*Axer-Siegel et al., 2007; Wikstrand et al., 2006*); however, the higher incidence of prematurity (*Axer-Siegel et al., 2005; Jafarzadehpur et al., 2013*) and twins (*Tornqvist et al., 2010*) in ART populations may play an important role. On the other hand, ART treatment was not found to affect IOP, axial length, anterior chamber depth, lens thickness (*Axer-Siegel et al., 2007*) and visual acuity (*Tornqvist et al., 2010; Wikstrand et al., 2006*) in the eyes of children born as a result of such treatment. Controversial data suggest abnormal retinal vascularization in ART children, especially boys (*Wikstrand et al., 2008*). The difference in the incidence of ROP in children born following ART treatment or conceived naturally was not significantly different in multiple births (*Barker et al., 2017*), although a higher proportion of babies requiring treatment was observed among twin ART offspring (*Barker et al., 2017*). Controversial data also exist regarding the risk of retinoblastoma in children born as a result of ART treatment. Some studies (*Källén et al., 2010; Marees et al., 2009; Moll et al., 2003*) showed increased risk, whereas other studies reported that risk was not significantly influenced by ART treatment (*Bradbury and Jick, 2004; Foix-L'Helias et al., 2012; Lidegaard et al., 2005*) but was related to many variables (confounders), such as time to pregnancy and/or maternal age (*Foix-L'Helias et al., 2012*).

Although 25 studies were included in this review, data were sparse and heterogeneous, and it was not possible to perform any data synthesis. In addition, the level and quality of the available evidence were suboptimal (evidence levels 3 or 4, low or very low for all of the outcomes considered in the present review quality; see **TABLE 3**). In fact, data available in the literature include retrospective and/or uncontrolled or not adequately controlled studies with evident recall bias (with potential misclassification), particularly for those performed after a long follow-up period (see *Radson et al., 2015*); studies with small populations (seven of 25 articles were case reports/case series) and studies with short follow-up evaluations; and present many confounders and biases including: heterogeneous populations (including patients with primary and secondary infertility, affected by mixed causes of infertility, with varying durations of infertility, who had received different numbers of infertility treatments previously, etc.), heterogeneous and mixed interventions (including IVF, ICSI, IUI, ovulation induction, oocyte/sperm donation or combinations) and protocols used for COH, confounding timing for ocular evaluation (e.g. ART women studied during pregnancy or babies born as a result of ART treatment studied at birth), and lack of data on the pregnancies (including obstetric management, maternal and/or perinatal complications). This last point is particularly important given the high risk of pregnancy complications detected in infertile patients who receive ART

treatment in terms of the risk of preterm birth and low birth weight (*Palomba et al., 2016a,b*). Unfortunately, no effort was made to contact the corresponding authors of the available studies in order to obtain more complete and detailed data, and this is clearly a limitation of this study.

As highlighted previously, in the available studies, the use of other complementary fertility drugs cannot be excluded during and before ART cycles. For example, the administration of clomiphene citrate has been associated with ocular disturbances (*Racette et al., 2010; Tunc, 2014*), and clomiphene citrate is frequently an initial therapeutic strategy for women with anovulatory infertility before ART treatment. The effect of clomiphene citrate could be sustained for subsequent cycles (*Palomba et al., 2006*). In addition, in such studies, oral contraceptives were used as pre-treatment before GnRH agonist administration (*Parihar et al., 2016*), and clomiphene citrate as co-treatment (*Yuksel et al., 2016*). Many mistakes were observed during careful reading of the included manuscripts regarding detailing of the drugs and protocols used for COH in ART cycles. For example, *Lee et al. (2010)* discussed the effects of oestrogen flare-up due to GnRHa, and focused their case on this event even if a GnRHant treatment (cetrorelix) was used.

A crucial confounder observed in such studies was evaluation of the main outcome measures in pregnant patients at the first post-treatment assessment. For example, data published by *Parihar et al. (2016)* included only ART patients who achieved a pregnancy, and all ocular assessments were performed at baseline and during the first trimester of pregnancy (post-treatment assessment) (*Parihar et al., 2016*). |However, it would be useful to assess the effects of ART treatment on ocular function and morphology before expected menses, or in patients who did not achieve a pregnancy.

At the present time, it is not known if infertility (commonly considered as time to pregnancy >12 months) impacts ocular function and morphology per se, or if it influences the potential effects of ART treatment on the eye. Similarly, relationships between factors of infertility [such as endometriosis or polycystic ovary syndrome (PCOS)] and ocular changes in function and morphology in women are also largely unknown. A few data suggest physiological and structural changes in the eyes of women with PCOS, particularly central corneal thickness (*Karaca Adıyeke et al., 2017*), and the meibomian and lacrimal glands (*Baser et al., 2017; Gonen et al., 2013*).

Several studies have demonstrated that the eye is a hormone-sensitive organ (see above), but to date it is not possible to distinguish between the effect of sex hormone changes during ART treatment on the eye and direct effects of drugs on specific ocular receptors. In addition, the changes in sex hormone levels are of very short duration during ART treatment, and it could be hypothesized that a clinically significant effect is seen only in the eyes of patients with previous ocular diseases and/or after repetitive ART cycles. Unfortunately, data on patients with previous ocular diseases and on the effects of repetitive ART cycles on the eye and visual function are very scarce. To this regard, *Yuksel et al. (2016)* demonstrated the effects of consecutive IVF treatments on the risk of progression of keratoconus.

In conclusion, the available data are inadequate to suggest or refute an influence of ART treatment on the eye, ocular function and ocular diseases in women who have undergone ART treatment and children born as a result of ART treatment. Well-designed prospective cohort studies with large samples are needed. Clearly, complete data on subjects' characteristics, interventions performed and precise timing of follow-up are crucial to obtain high-quality clinical evidence. In particular, data on the eyes of children born as a result of ART treatment should be obtained, with attention given to obstetric and perinatal data, and the findings for the main confounders, such as gestational age, birth weight and singletons/twins, should be stratified and adjusted.

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Received 20 June 2018; received in revised form 23 September 2018; accepted 29 November 2018.