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DOI:

[10.5301/ejo.5000832](https://doi.org/10.5301/ejo.5000832)

*Document Version*

Peer reviewed version

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*Citation for published version (APA):*

Barker, L., Bunce, C., Husain, S., & Adams, G. G. W. (2017). Is artificial reproductive technology a risk factor for retinopathy of prematurity independent of the generation of multiple births? *European Journal of Ophthalmology*, 174-178. <https://doi.org/10.5301/ejo.5000832>

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**Is artificial reproductive technology a risk factor for retinopathy of prematurity independent of the generation of multiple births?**

**Short title:** Artificial reproductive technology and retinopathy of prematurity

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## **Abstract**

**Purpose:** There is some debate regarding whether artificial reproductive technology (ART) constitutes an independent risk factor for retinopathy of prematurity (ROP). We wanted to assess the prevalence of ART in multiple birth infants seen for ROP screening and whether or not ROP was identified or treated, in order to evaluate whether ART contributes a risk factor for ROP independent of the generation of multiple births.

**Methods:** A retrospective audit was performed of all multiple birth babies admitted to a tertiary Neonatal unit who met the UK ROP screening criteria (<32 weeks gestational age (GA) and/or <1501g birth weight (BW)).

**Results:** 205 babies met our criteria of which 87.3% were twins. 39.5% were born following ART. 30.5% of the non-ART group developed ROP versus 34% of the ART group ( $P=0.837$ ). Stage 3 ROP developed in 5.1% non-ART babies and 6% ART babies. 8.5% non-ART babies and 10% ART babies required treatment for ROP. Logistic regression demonstrated that ART was not independently associated with development of ROP.

**Conclusions:** ART multiple birth babies make up a considerable proportion of the ROP screening burden and their number is likely to increase as ART is increasingly available and utilised. We found no significant difference between the numbers of babies developing ROP in the ART versus non-ART groups, but the numbers are small. The estimated odds of developing ROP is slightly higher in the ART babies so our data do not rule out a possible association.

Keywords: Artificial reproductive technology; Multiple births, Retinopathy of prematurity

# **Is artificial reproductive technology a risk factor for retinopathy of prematurity independent of the generation of multiple births?**

**Barker L, Husain S, Bunce C, Adams G**

## Introduction

Artificial reproductive technology (ART) has been responsible for an increased rate of both premature and multiple births in the UK since the birth of the first in vitro fertilisation (IVF) baby in 1978. ART increases the risk of preterm birth both independently and by increasing the risk of multiple births whereby babies are more likely to be born earlier and smaller (1,2,3,4). In recognition of the increased morbidity and mortality associated with these risks the UK's Human Fertility and Embryology Association (HFEA) and British Fertility Society (BFS) introduced guidance in 2008 encouraging the use of elective single embryo transfer (eSET) in mothers at greatest risk of multiple birth (5). In older mothers, where the risk is lower, it was recommended that no more than two embryos should be transferred. These recommendations have been shown elsewhere in Europe to maintain the live birth rates following IVF but significantly lower the rate of multiple births, particularly of higher plurality (6). In 2015, the HFEA published a report detailing a significant reduction in the rate of multiple birth pregnancies in the UK since the publication in 2008, reduced from 1 in 4 in 2008 to 1 in 6 in 2013 (7). During this time period, the overall rate of successful pregnancies actually increased slightly from 30% to 34% and eSET use had

markedly increased from less than 5% patients to 29%. This reduction in iatrogenic multiple births is significant when one considers the increased rate of morbidity in babies born from multiple pregnancies.

All babies who are born significantly premature are at risk of retinopathy of prematurity (ROP). The risk increases in multiple births due to the increased rate of lower gestational age and birth weight. It is unclear whether ART, and IVF in particular, represents an independent risk factor for neonatal morbidity, in particular, ROP. Studies have demonstrated a positive, negative or neutral effect of ART on neonatal outcomes (8,9,10). Whilst it has been suggested that the process and results of IVF may represent an independent risk factor for ROP, others have concluded that it is simply the increased rates of prematurity and low birth weight which generate the higher rates of ROP in children born following ART (11,12).

In 1996, McKibbin & Dabbs noted that of the babies born following ART at St James's University Hospital, Leeds, 59 (20.3%) met the criteria for retinopathy of prematurity (ROP) screening and 56 (94.9%) of those were multiple births (33.9% twins, 66.1% triplets) (13). Of these 56 babies, 22.7% developed ROP and 4.5% required treatment. Funnell & Dabbs repeated the audit in 2007, prior to the change in HFEA guidance, and found that only 4.2% (11/265) of those who met the screening criteria were born following ART, comprising 3 singletons and 4 sets of twins (14). None of these babies developed ROP. This significant

reduction in the proportion of ART multiple births seen for ROP screening, can be at least partly attributed to technological advances in fertility treatment allowing fewer embryos to be transferred during treatment without compromising the success rates. It remained the norm however, at this time point, to transfer more than one embryo in order to maximise the chance of a successful implantation and subsequent pregnancy.

The purpose of this study was to assess the situation regarding multiples in our ROP screening population, in particular, the prevalence of ART in multiple birth infants seen for ROP screening and whether or not ROP was identified or treated, in order to evaluate whether ART contributes a risk factor for ROP independent of the generation of multiple births.

## Methods

A retrospective audit was performed in the tertiary Neonatal Unit of Homerton University Hospital NHS Foundation Trust (HUH). All live births at HUH between January 2007 and December 2011 inclusive who met the RCOphth screening criteria (babies born <32 weeks and/or < 1501g) were identified using a neonatal database housed by the BadgerNet Platform (<http://www.clevermed.com>). This database, used by the majority of neonatal units in the UK, captures a number of parameters including gestational age at birth (GA) and birth weight (BW). The audit was performed with the permission of HUH's Clinical Audit Department.

Data from multiple births who met the ROP screening criteria were extracted from hospital clinical notes and databases. Data collected included maternal age and self-reported ethnicity, the baby's GA, BW, and presence of major congenital anomalies, mode of conception (spontaneous or assisted), type of ART, plurality, and ROP screening outcome.

Study characteristics were summarised by spontaneous conception versus ART using means and standard deviations for continuous data and numbers with proportions for categorical data. Group differences were assessed using Fisher's exact test for categorical variables and t-tests for continuous variables. Logistic regression was used to identify whether the odds of having ROP were associated with ART.

## Results

There were 24,229 live births at HUH in the 5-year audit period. Of these, 1015 (4.2%) were multiple births. In total, 1272 (5.2%) babies met the ROP screening criteria; 205 (16.1%) of these were multiple births. 20.2% multiple birth babies met the screening criteria versus 4.6% singleton babies. Data completeness was 100%.

Focussing on the multiple births babies who met the screening criteria, the average maternal age was 31 years (SD 6.7 years; range 18-50). Self-reported maternal ethnicity was White British/Irish in 83 (41%), Black/Black British in 41 (20%), Asian/Asian British in 41 (20%), Other in 27 (12.7%); in 13 (6.3%) no ethnicity was recorded.

The mean gestational age of the babies was 28 weeks (range 22-35 weeks) and mean birth weight was 1063g (range 338-1845g). Of the 205 multiple births, 106 (51.7%) were male, 179 (87.3%) were twins, 21 (10.2 %) were triplets and 5 (2.4%) were quintuplets.

Eighty-one babies (39.5%) were born following ART with the remainder being spontaneous conceptions. Of those born following ART, 69 (86.3%) were born following IVF (3 of these also used a donor egg), 2 (2.5%) following intracytoplasmic sperm injection (ICSI) and 9 (11.1%) using Clomifene. The mean gestational age in both the assisted and spontaneous conception groups was the same at 28.3 weeks and there was no significant difference between the birth weights ( $P = 0.28$ ). The characteristics of both groups can be seen in table 1.

Twenty-one babies (10.3%) died before ROP screening commenced. One hundred and eight (53%) of the babies were screened at HUH, 1 was screened elsewhere before transfer in to the unit for medical reasons (included in the study

as full ROP details were available), 1 baby failed to attend their screening appointment twice and the remainder were transferred elsewhere prior to screening. There was no difference between babies screened and not screened in relation to maternal age or ethnicity. Of those babies screened for ROP at HUH, 35 were found to have ROP of any stage; 30.5% of the spontaneous conception babies and 34% of the ART babies (see table 2). This difference was not statistically significant ( $P=0.837$ ).

Stage 3 ROP developed in 6% ART babies and 5.1% of the spontaneously conceived babies. In total, 10 babies required treatment for ROP; 5 (8.5%) of the spontaneously conceived group and 5 (10%) of the ART group. The proportions of babies in each stage did not differ between ART and non ART babies ( $P=0.93$ ).

Using logistic regression, we found that BW and GA were significantly associated with the development of any ROP whereas ART was not (Table 3).

## Discussion

Our results show that 4.2% live births at our centre during this study period were multiple births and infants born from a multiple pregnancy constituted 16.1% of the ROP screening population. ART was the mode of conception in 39% of multiple births eligible for ROP screening and multiple birth babies born as a

result of ART made up 6.3% of our total screening population. Although we would expect to see a continuing reduction in the number of multiple births in the UK given the 2015 HFEA report, this group remains relatively sizeable and may continue to increase as the availability of ART increases and its use becomes more commonplace due to the trend of women leaving motherhood until later in life (7).

Over the five years covered by the audit, the rate of multiple pregnancies in England and Wales increased slightly, from 15.3 per 1000 births in 2007 to 16.1 in 2011 (15). Higher order multiples (triplets and above) have remained static over this period (1.4% all multiple births in 2006 and 1.5% in 2011) (16,17). Elsewhere in the world, a downward trend in higher order multiples has been observed. Bassil et al (2012) found the rate of triplet birth significantly decreased between 2003 and 2008 in Canada whereas the number of pre-term twins increased (18). Due to advances in healthcare and technology, neonatal outcomes improved over this time period in these Canadian infants, including a reduction in the rate of severe ROP.

We found the rates of higher order multiple births to be lower than in the 1996 study by McKibben and Dabbs study but higher than that of the follow-up study by Funnell and Dabbs (13,14). We had one set of quintuplets following fertility treatment in another country, but the rate of triplets following ART was 5% compared to 66.1% in the study by McKibben and Dabbs and 0% in Funnell and

Dabbs (13,14). It is worth noting however, that the latter study was conducted over a 40-month period versus our 60-month study. It is perhaps of concern that the rate of higher plurality births might be increasing again although we found that several of our mothers, particularly when the maternal age was significantly higher than average, went abroad for their IVF treatment to countries where the regulation of fertility treatment is less strict than that in the UK, returning to the UK to deliver their babies.

We found no significant difference between the numbers of babies developing ROP in the ART versus non-ART groups, but the numbers are small. The estimated odds of developing ROP is slightly higher in the ART babies with an odds ratio of 1.17 (0.52, 2.63) and an adjusted (for BW) OR of 1.23 (0.497, 3.04) so our data do not rule out a possible association. Also, 74 of the 205 babies who met the screening criteria were transferred elsewhere prior to the start of their screening. Although it is likely that they would have been transferred back to the unit for treatment should this have been necessary due to the referral pathway in the region, we cannot comment on the presence or severity of ROP in this group.

There is dispute in the literature regarding the role of ART as a risk factor for ROP. Watts & Adams (2000) reported a disproportionately high rate of ART in their ROP treated population (28.6%) compared to their ROP screened population (11.7%)(11). Shah et al (2011) reported that, once corrected for

confounding variables, the mode of conception had no detectable effect on composite neonatal outcomes including advanced ROP (19). It is well established that the most significant risk factors for development of ROP are low BW and GA and there appears to be a higher rate of early pre-term delivery (GA < 32 weeks) and low BW in the ART population which may account for the higher rates of ROP seen (3,12,20). Our audit found no difference between BW and GA of babies in the ART and spontaneous conception groups, meaning we cannot exclude ART as an additional risk factor although it is noteworthy that we did not collect data, and therefore cannot comment, on other risk factors for ROP such as neonatal co-morbidity and poor weight gain.

Another factor, which may be of significance, is the proportion of mono- and dizygotic twins within the study population. Given the technique of IVF, it is obvious that most twins born following ART will be dizygotic however a small proportion (<2%) are monozygotic and Vitthala et al (2009) have identified a significantly higher rate of monozygotic twins following ART than spontaneous conception in their meta-analysis (7,21). As the majority of monozygotic twins are monozygotic, with a known increased rate of perinatal morbidity and mortality, it is possible that this plays a significant role in the development of any ROP by increasing the vulnerability of the developing foetuses (22). The identical genetics of monozygotic twins may also be of relevance given the evidence to suggest a genetic influence in the development of ROP (23). We did

not gather data on the zygosity of our infants and suggest that further work is needed in this area.

In 2011, a Canadian study identified an “epidemic of multiple gestations” due to the practice of multiple embryo transfer in IVF and found that 17% NICU admissions over a 2-year period were multiple birth infants born after ART (24). Extrapolating the figures, they identified what was described as the “cost of irresponsibility” and concluded that eSET could prevent 30-40 neonatal deaths and between 13-19 retinal procedures per year without jeopardising the success rate of IVF treatment. In Sweden, eSET has been the norm since 2000. Kallen et al (2010) reported on the IVF outcome trends over a 5-year period in Sweden and found, on a background of a stable IVF success rate, not only a decrease in multiple birth rate to around 5%, but also significant improvements in the health outcomes of both mother and child (6). Boulet et al (2008) noted no increase in neonatal morbidity in post ART twins compared to spontaneously conceived twins in the US; however, they did conclude that the higher risks associated with multiple births could be avoided by the promotion of singleton gestation in ART (25).

Multiple births made up 16.1% of our ROP screening load. This figure is similar to those reported from Italy (13.4%) and the US (17%)(26,28). However, it represents a smaller screening burden compared to other international studies (see table 4). Whilst it is possible that this is due to differences in fertility

treatment guidelines and availability, it should be noted that the percentage of multiple birth infants born following ART is similar across the international literature (see table 4).

Since the launch of the HFEA's "One at a time" campaign in 2009, increasing use of eSET in UK IVF clinics has seen the multiple birth rate fall from 27% to close to 16% whilst the overall successful pregnancy rate increases from 30% to 34%(7). This has caused a reduction in higher order multiple births and a subsequent reduction in the ROP screening burden overall. In February 2013, NICE guidelines were published echoing the recommendation to use eSET in healthy, younger mothers where the risk of multiple birth following multiple embryo transfer remains high and the 2015 HFEA report results demonstrate the successful collaboration between the HFEA, fertility clinics and practitioners, all keen to reduce the rate of iatrogenic multiple births. Due to a legal challenge however, since January 2014, UK fertility clinics have been no longer subject to a condition on their licence that they maintain their multiple birth rate below a centrally dictated target. This raises the possibility that we might expect to see the multiple birth and higher plurality rates increasing once again as clinics transfer more embryos in order to achieve higher success rates in the competitive world of fertility medicine. As such, paediatric ophthalmologists might expect an increase in both their screening workload and the numbers of babies requiring ROP treatment over the months and years to come.

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	Spontaneous conception	ART	
Total, number	124	81	
Gestational age (weeks), mean (SD)	28.3 (2.5)	28.3 (3.0)	
Birth weight (grams), mean (SD)	1043 (290)	1093 (360)	
Maternal age (years), mean (SD)	28.9 (5.4)	34.5 (7.2)	
Ethnicity, number (%)	White/British	44 (35.5%)	39 (48.1%)
	Asian/Asian	28 (22.6%)	13 (16.1%)
	British		
	Black/Black	26 (21.0%)	15 (18.5%)
	British		
	Mixed	3 (2.4%)	1 (1.2%)
	Other	17 (13.7%)	6 (7.3%)
Not disclosed	6 (4.8%)	7 (8.6%)	

Table 1: Summary of the two groups

	Spontaneous conception	ART
Total screened	59	50
Worst ROP found	0 41 (69.5%)	33 (66%)
during screening,	1 5 (8.5%)	6 (12%)
number (%)	2 10 (16.9%)	8 (16%)
	3 3 (5.1%)	3 (6%)
Any ROP	18 (30.5%)	17 (34%)
Required treatment	5 (8.5%)	5 (10%)

Table 2: Worst ROP seen during screening

	Odds Ratio	95% Confidence Intervals	P value
Birth weight (per gram)	0.996	0.994 to 0.998	< 0.001
ART	1.173	0.524 to 2.627	0.697
Gestational age	0.571	0.458 to 0.71	< 0.001

Table 3: Logistic regression exploring associations between development of any ROP and baseline factors

	Years studied	Country	Number within screening criteria*	Multiple birth babies within screening criteria; number (%)	SC multiples screened; number (%)	ART multiples screened; number (%)
Current study	2007-2011	UK	1272	205 (16.1%)	124 (60.5%)	81 (39.5%)
Blumenfeld et al 1998[26]	1992-1995	USA	840	149 (17%)		
Garg et al 2010[27]	1994-2005	Australia	10,068	2764 (27.5%)		
Corchia et al 2014[28]	2003-2005	Italy	2934	407 (13.9%)	288 (70.8%)	119 (29.2%)
Shah et al 2011[19]	2005-2008	Canada	1130	370 (32.7%)	233 (63%)	137 (37%)
Picaud et al 2012[8]	2003-2007	France	649**	240 (37%)**		

Table 4: Comparison of data to international literature. \*Total number of babies <32 weeks and/or <1501g regardless of screening criteria quoted in the study.

\*\*Included 37 triplets excluded from data analysis.